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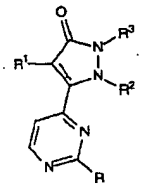

(A)

(57) Abstract: The present invention relates to compounds which are capable of preventing the extracellular release of inflammatory cytokines, said compounds, or enantiomeric and diasteriomeric forms or pharmaceutically acceptable salts thereof, have the formula: (A) wherein R is an ether or amino unit, R1 is substituted phenyl, each R2 and R3 unit is independently selected from the group consisting of: a) hydrogen; and b) substituted or unsubstituted C1-C10 hydrocarbyl selected from the group consisting of: i) C1-C10 linear, branched or cyclic alkyl; ii) C1-C10 aryl; iii) C1-C10 heterocyclic; iv) C1-C10 heteroaryl.

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1,2-DIHYDROPYRAZOL-3-ONES AS CYTOKINE MEDIATORS

FIELD OF THE INVENTION

The present invention relates to 1,2-dihydropyrazol-3-ones which inhibit the extracellular release of inflammatory cytokines, said cytokines responsible for one or more human or higher mammalian disease states. The present invention further relates to compositions comprising said 1,2-dihydropyrazol-3-ones and method for preventing, abating, or otherwise controlling enzymes which are understood to be the active components responsible for the herein described disease states.

BACKGROUND OF THE INVENTION

Interleukin –1 (IL-1) and Tumor Necrosis Factor-α (TNF-α) are among the important biological substances known collectively as "cytokines." These molecules are understood to mediate the inflammatory response associated with the immunological recognition of infectious agents.

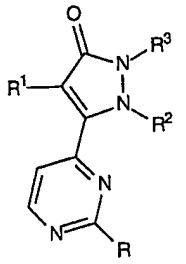
These pro-inflammatory cytokines are suggested as an important mediators in many disease states or syndromes, *inter alia*, rheumatoid arthritis, osteoarthritis, inflammatory bowel disease (IBS), septic shock, cardiopulmonary dysfunction, acute respiratory disease, cachexia, and therefore responsible for the progression and manifestation of human disease states.

There is therefore a long felt need for compounds and pharmaceutical compositions which comprise compounds, which can block, abate, control, mitigate, or prevent the release of cytokines from cells which produce them

SUMMARY OF THE INVENTION

The present invention meets the aforementioned needs in that it has been surprisingly found that certain bicyclic pyrazolones and derivatives thereof are effective for inhibiting release of inflammatory cytokines, *inter alia*, interleukin-1 (IL-1) and tumor necrosis factor (TNF) from cells and thereby preventing, abating, or otherwise controlling enzymes which are proposed to be the active components responsible for the herein described disease states.

The first aspect of the present invention relates to compounds, including all enantiomeric and diasteriomeric forms and pharmaceutically acceptable salts thereof, said compounds having the formula:



wherein R is:

a) $-O[CH_2]_nR^4$; or

b) $-NR^{5a}R^{5b}$;

R^4 is substituted or unsubstituted C_1-C_{10} linear, branched, or cyclic alkyl; substituted or unsubstituted aryl; substituted or unsubstituted heterocyclic; or substituted or unsubstituted heteroaryl; the index n is from 0 to 5;

R^{5a} and R^{5b} are each independently:

a) hydrogen; or

b) $-[C(R^{6a}R^{6b})]_mR^7$;

each R^{6a} and R^{6b} are independently hydrogen, $-OR^8$, $-N(R^8)_2$, $-CO_2R^8$, $-CON(R^8)_2$; C_1-C_4 linear, branched, or cyclic alkyl, and mixtures thereof; R^7 is hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted heterocyclic, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; $-OR^8$, $-N(R^8)_2$, $-CO_2R^8$, $-CON(R^8)_2$; R^8 is hydrogen, a water-soluble cation, C_1-C_4 alkyl, or substituted or unsubstituted aryl; the index m is from 0 to 5;

R^1 is substituted phenyl;

each R^2 and R^3 unit is independently selected from the group consisting of:

a) hydrogen; and

b) substituted or unsubstituted C_1-C_{10} hydrocarbyl selected from the group consisting of:

i) C_1-C_{10} linear, branched or cyclic alkyl;

ii) C_6-C_{10} aryl;

iii) C_1-C_{10} heterocyclic;

iv) C_1-C_{10} heteroaryl.

Another aspect of the present invention relates to pharmaceutical compositions which can deliver the compounds of the present invention to a human or higher mammal, said compositions comprising:

a) an effective amount of one or more of the compounds according to the present invention; and

b) one or more pharmaceutically acceptable excipients.

A further aspect of the present invention relates to methods for controlling one or more inflammatory cytokine mediated or inflammatory cytokine modulated mammalian diseases or

conditions, said method comprising the step of administering to a human or higher mammal and effective amount of a composition comprising one or more of the compounds according to the present invention.

Another aspect of the present invention relates to forms of the compounds of the present invention, which under normal physiological conditions, will release the compounds as described herein.

These and other objects, features, and advantages will become apparent to those of ordinary skill in the art from a reading of the following detailed description and the appended claims. All percentages, ratios and proportions herein are by weight, unless otherwise specified. All temperatures are in degrees Celsius (^{o} C) unless otherwise specified. All documents cited are in relevant part, incorporated herein by reference; the citation of any document is not to be construed as an admission that it is prior art with respect to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compounds which are capable of mediating, controlling or otherwise inhibiting the extracellular release of certain cytokines, especially inflammatory cytokines, said cytokines playing a role in the stimulation, cause or manifestation of a wide variety of diseases, disease states, or syndromes.

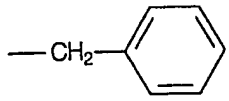
For the purposes of the present invention the term "hydrocarbyl" is defined herein as any organic unit or moiety which is comprised of carbon atoms and hydrogen atoms. Included within the term hydrocarbyl are the heterocycles which are described herein below. Examples of various unsubstituted non-heterocyclic hydrocarbyl units include pentyl, 3-ethyloctanyl, 1,3-dimethylphenyl, cyclohexyl, cis-3-hexyl, 7,7-dimethylbicyclo[2.2.1]-heptan-1-yl, and naphth-2-yl.

Included within the definition of "hydrocarbyl" are the aromatic (aryl) and non-aromatic carbocyclic rings, non-limiting examples of which include cyclopropyl, cyclobutanyl, cyclopentanyl, cyclohexane, cyclohexenyl, cycloheptanyl, bicyclo-[0.1.1]-butanyl, bicyclo-[0.1.2]-pentanyl, bicyclo-[0.1.3]-hexanyl (thujanyl), bicyclo-[0.2.2]-hexanyl, bicyclo-[0.1.4]-heptanyl (caranyl), bicyclo-[2.2.1]-heptanyl (norboranyl), bicyclo-[0.2.4]-octanyl (caryophyllenyl), spiropentanyl, diclyclopentanespiranyl, decalinyl, phenyl, benzyl, naphthyl, indenyl, 2H-indenyl, azulenyl, phenanthryl, anthryl, fluorenyl, acenaphthylenyl, 1,2,3,4-tetrahydronaphthalenyl, and the like.

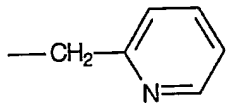
The term "heterocycle" includes both aromatic (heteroaryl) and non-aromatic heterocyclic (heterocyclic) rings non-limiting examples of which include: pyrrolyl, 2H-pyrrolyl, 3H-pyrrolyl, pyrazolyl, 2H-imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, isoxazolyl, oxazoyl, 1,2,4-oxadiazolyl, 2H-pyranyl, 4H-pyranyl, 2H-pyran-2-one-yl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, s-triazinyl, 4H-1,2-oxazinyl, 2H-1,3-oxazinyl, 1,4-oxazinyl, morpholinyl, azepinyl, oxepinyl, 4H-1,2-diazepinyl, indenyl 2H-indenyl, benzofuranyl, isobenzofuranyl, indolyl, 3H-indolyl, 1H-indolyl,

benzoxazolyl, 2H-1-benzopyranyl, quinolinyl, isoquinolinyl, quinazolinyl, 2H-1,4-benzoxazinyl, pyrrolidinyl, pyrrolinyl, quinoxalinyl, furanyl, thiophenyl, benzimidazolyl, and the like each of which can be substituted or unsubstituted.

An example of a unit defined by the term "alkylenearyl" is a benzyl unit having the formula:



whereas an example of a unit defined by the term "alkyleneheteroaryl" is a 2-picolyl unit having the formula:



The term "substituted" is used throughout the specification. The term "substituted" is defined herein as "encompassing moieties or units which can replace a hydrogen atom, two hydrogen atoms, or three hydrogen atoms of a hydrocarbyl moiety. Also substituted can include replacement of hydrogen atoms on two adjacent carbons to form a new moiety or unit." For example, a substituted unit that requires a single hydrogen atom replacement includes halogen, hydroxyl, and the like. A two hydrogen atom replacement includes carbonyl, oximino, and the like. A two hydrogen atom replacement from adjacent carbon atoms includes epoxy, and the like. Three hydrogen replacement includes cyano, and the like. An epoxide unit is an example of a substituted unit which requires replacement of a hydrogen atom on adjacent carbons. The term substituted is used throughout the present specification to indicate that a hydrocarbyl moiety, *inter alia*, aromatic ring, alkyl chain, can have one or more of the hydrogen atoms replaced by a substituent. When a moiety is described as "substituted" any number of the hydrogen atoms may be replaced. For example, 4-hydroxyphenyl is a "substituted aromatic carbocyclic ring", (N,N-dimethyl-5-amino)octanyl is a " substituted C_8 alkyl unit, 3-guanidinopropyl is a "substituted C_3 alkyl unit," and 2-carboxypyridinyl is a "substituted heteroaryl unit." The following are non-limiting examples of units which can serve as a replacement for hydrogen atoms when a hydrocarbyl unit is described as "substituted."

i) $-[C(R^{13})_2]_p(CH=CH)_qR^{13}$;

ii) $-[C(R^{13})_2]_pC(Z)R^{13}$;

iii) $-[C(R^{13})_2]_pC(Z)_2R^{13}$;

iv) $-[C(R^{13})_2]_pC(Z)CH=CH_2$;

v) $-[C(R^{13})_2]_pC(Z)N(R^{13})_2$;

vi) $-[C(R^{13})_2]_pC(Z)NR^{13}N(R^{13})_2$;

vii) $-[C(R^{13})_2]_pCN$;

viii) $-[C(R^{13})_2]_pCNO$;

ix) $-[C(R^{13})_2]_pCF_3$, $-[C(R^{13})_2]_pCCl_3$, $-[C(R^{13})_2]_pCBr_3$;

Z) $-[C(R^{13})_2]_pN(R^{13})_2$;

xi) $-[C(R^{13})_2]_pNR^{13}CN$;

xii) $-[C(R^{13})_2]_pNR^{13}C(Z)R^{13}$;

xiii) $-[C(R^{13})_2]_pNR^{13}C(Z)N(R^{13})_2$;

xiv) $-[C(R^{13})_2]_pNHN(R^{13})_2$;

xv) $-[C(R^{13})_2]_pNHOR^{13}$;

xvi) $-[C(R^{13})_2]_pNCS$;

xvii) $-[C(R^{13})_2]_pNO_2$;

xviii) $-[C(R^{13})_2]_pOR^{13}$;

xix) $-[C(R^{13})_2]_pOCN$;

xx) $-[C(R^{13})_2]_pOCF_3$, $-[C(R^{13})_2]_pOCCl_3$, $-[C(R^{13})_2]_pOCBr_3$;

xxi) $-[C(R^{13})_2]_pF$, $-[C(R^{13})_2]_pCl$, $-[C(R^{13})_2]_pBr$, $-[C(R^{13})_2]_pI$, and mixtures thereof;

xxii) $-[C(R^{13})_2]_pSCN$;

xxiii) $-[C(R^{13})_2]_pSO_3M$;

xxiv) $-[C(R^{13})_2]_pOSO_3M$;

xxv) $-[C(R^{13})_2]_pSO_2N(R^{13})_2$;

xxvi) $-[C(R^{13})_2]_pSO_2R^{13}$;

xxvii) $-[C(R^{13})_2]_pP(O)H_2$;

xxviii) $-[C(R^{13})_2]_pPO_2$;

xxix) $-[C(R^{13})_2]_pP(O)(OH)_2$;

xxx) and mixtures thereof;

wherein R^{13} is hydrogen, substituted or unsubstituted C_1-C_{20} linear, branched, or cyclic alkyl, C_6-C_{20} aryl, C_7-C_{20} alkylenearyl, and mixtures thereof; M is hydrogen, or a salt forming cation; Z is =O, =S, $=NR^{13}$, and mixtures thereof; p is from 0 to 12; q is from 0 to 12. Suitable salt forming cations include, sodium, lithium, potassium, calcium, magnesium, ammonium, and the like.

1,2-dihydropyrazol-3-ones

The present invention relates to 1,2-dihydropyrazol-3-ones which inhibit the extracellular release of inflammatory cytokines. The compounds of the present invention comprise three elements. The first is the core 1,2-dihydropyrazol-3-one ring scaffold which can be substituted or unsubstituted as described herein below at the nitrogen atoms that comprise the ring system 1-position and 2-position. The second element is the 5-position pyrimidine ring attached at the 4-position of the pyrimidine ring and further substituted at the pyrimidine ring 2-position by either an ether group or an amino group. The third element is a substituted phenyl group at the ring scaffold 4-position. The following is a description of the compounds comprising the present invention.

R is a substituent at the 2-position of the pyrimidin-4-yl portion of the general scaffold, said R unit is:

a) an ether having the formula $-O[CH_2]_nR^4$; or

b) an amino unit having the formula $-NR^{5a}R^{5b}$;

wherein R^4 is substituted or unsubstituted C_1-C_{10} linear, branched, or cyclic alkyl; substituted or unsubstituted C_6-C_{10} aryl; substituted or unsubstituted C_1-C_{10} heterocyclic; or substituted or unsubstituted C_1-C_{10} heteroaryl; the index n is from 0 to 5.

The following are the various aspects of R units according to the present invention wherein R is an ether having the formula $-O[CH_2]_nR^4$. However, the formulator is not limited to the herein exemplified iterations and examples.

A) R units encompassing ethers having the formula $-OR^4$ (the index n equal to 0) and R^4 is substituted or unsubstituted aryl.

i) One iteration of this aspect of R comprises ethers having the formula $-OR^4$ and R^4 is substituted or unsubstituted aryl. This iteration includes the following non-limiting example of R: phenoxy, 2-fluorophenoxy, 3-fluorophenoxy, 4-fluorophenoxy, 2,4-difluorophenoxy, 3-trifluoromethylphenoxy, 4-trifluoromethylphenoxy, 2,4-trifluoromethyl phenoxy, and the like.

ii) Another iteration of this aspect of R comprises ethers having the formula $-OR^4$ and R^4 is substituted or unsubstituted aryl. This iteration includes the following non-limiting examples: 2-methylphenoxy, 3-methylphenoxy, 4-methylphenoxy, 2,4-dimethylphenoxy, 2-cyanophenoxy, 3-cyanophenoxy, 4-cyanophenoxy, 4-ethylphenoxy, and the like.

iii) A further iteration of this aspect of R comprises ethers having the formula $-OR^4$ and R^4 is substituted or unsubstituted aryl. This iteration includes the following non-limiting examples: (2-methyoxy)phenoxy, (3-methoxy)phenoxy, (4-methoxy)phenoxy, 3-[(N-acetyl)amino]phenoxy, 3-benzo[1,3]dioxol-5-yl, and the like.

B) R units encompassing ethers having the formula $-OR^4$ (the index n equal to 0) and R^4 is substituted or unsubstituted heteroaryl.

i) A first iteration of this aspect of R comprises ethers having the formula $-OR^4$ and R^4 is unsubstituted heteroaryl. This iteration includes the following non-limiting examples: pyrimidin-2-yl, pyrimidin-4-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, and the like.

ii) A second iteration of this aspect of R comprises ethers having the formula $-OR^4$ and R^4 is substituted heteroaryl. This iteration includes the following non-limiting examples: 2-aminopyrimidin-4-yl, and the like.

C) R units encompassing ethers having the formula $-OCH_2R^4$ (the index n equal to 1) and R^4 is substituted or unsubstituted aryl.

i) A first iteration of this aspect of R comprises ethers having the formula $-OCH_2R^4$ and R^4 is substituted or unsubstituted heteroaryl. This iteration includes the following non-limiting examples: pyrimidin-2-yl, pyrimidin-4-yl, 2-aminopyrimidin-4-yl, 4-aminopyrimidin-6-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, and the like.

ii) A second iteration of this aspect of R wherein R is an ether having the formula $-OCH_2R^4$ and R^4 is substituted or unsubstituted alkyleneheteroaryl-aryl. This iteration includes the following non-limiting examples: pyridin-3-ylethyl, (2-methyl-2-pyridin-3-yl)ethyl, and the like.

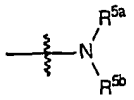
D) R units encompassing ethers having the formula $-OR^4$ (the index n equal to 1) and R^4 is substituted or unsubstituted C_1-C_4 alkyl or a C_3-C_{10} carbocyclic unit.

i) A first iteration of this aspect of R is an ether having the formula $-OR^4$ and R^4 is unsubstituted C_1-C_4 linear, branched, or cyclic alkyl. This iteration includes the following non-limiting examples: methyl, ethyl, isopropyl, (*S*)–1-methypropyl, and the like.

ii) A second iteration of this aspect of R is an ether having the formula $-OR^4$ and R^4 is a substituted C_1-C_4 linear, branched, or cyclic alkyl. This iteration includes the following non-limiting examples: 2-methoxyethyl, (*S*)–1-methy-3-methyoxypropyl, and the like.

iii) A third iteration of this aspect of R is an ether having the formula $-OR^4$ and R^4 is a substituted or unsubstituted C_3-C_{10} carbocyclic unit. This iteration includes cyclopropyl, cyclopentyl, 2,5-dimethylcyclopentyl, cyclohexyl, and the like.

The following are non-limiting examples of the various aspects of R units according to the present invention wherein R comprises an amino unit having the formula:



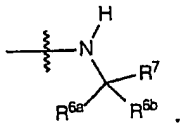
wherein R^{5a} and R^{5b} are each independently:

a) hydrogen; or

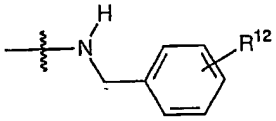
b) $-[C(R^{6a}R^{6b})]_mR^7$;

each R^{6a} and R^{6b} are independently hydrogen, substituted or unsubstituted C_1-C_4 linear, branched, or cyclic alkyl, $-OR^8$, $-N(R^8)_2$, $-CO_2R^8$, $-CON(R^8)_2$; and mixtures thereof; R^7 is hydrogen, substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl, substituted or unsubstituted heterocyclic, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; $-OR^8$, $-N(R^8)_2$, $-CO_2R^8$, $-CON(R^8)_2$; R^8 is hydrogen, a water-soluble cation, C_1-C_4 alkyl, or substituted or unsubstituted aryl; the index m is from 0 to 5. However, the formulator is not limited to the following exemplified iterations and examples.

A) R units encompassing racemic amino groups wherein R^{5a} is hydrogen, R^{6a} or R^{6b} is hydrogen or C_1-C_4 alkyl, and R^7 is substituted or unsubstituted aryl or heteroaryl, said units having the formula:

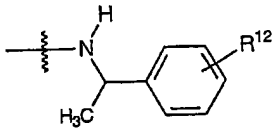


i) A first iteration of this aspect includes units wherein both R^{6a} and R^{6b} are each hydrogen and R^7 is aryl or substituted aryl, said units having the formula:



Non-limiting examples of this iteration include benzylamino, (4-fluorobenzyl)amino, (2-amino-benzyl)amino, (2-methylbenzyl)amino, (4-methylbenzyl)amino, (4-methoxybenzyl)amino, (4-methanesulfonyl)benzylamino, and (4-propanesulfonyl)benzylamino.

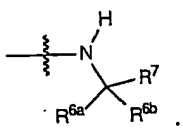
ii) A second iteration of this aspect includes units wherein one unit of R^{6a} and R^{6b} is hydrogen and the other is methyl, R^7 is aryl or substituted aryl, said unit having the formula:



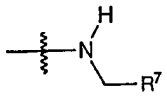
Non-limiting examples of this iteration include (α)-methylbenzylamino, and 1-(4-fluorophenyl)-ethylamino.

iii) A third iteration of this aspect includes units wherein both R^{6a} and R^{6b} are each hydrogen and R^7 is heteroaryl or substituted heteroaryl. Non-limiting examples of this iteration include (pyridin-2-yl)methylamino, (pyridin-3-yl)methylamino, (pyridin-4-yl)methylamino, and (imidazol-2-yl)methylamino.

B) R units encompassing racemic amino groups wherein R^{5a} is hydrogen, R^{6a} or R^{6b} is hydrogen or C_1-C_4 alkyl, and R^7 is substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl, said units having the formula:

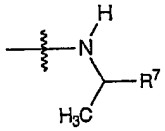


i) A first iteration of this aspect includes units wherein both R^{6a} and R^{6b} are each hydrogen and R^7 is hydrogen or C_1-C_6 linear, branched, or cyclic alkyl.



Non-limiting examples of this iteration include methylamino, ethylamino, propylamino, *iso*-butylamino, and cyclopropylmethylamino.

ii) A second iteration of this aspect includes units wherein one unit of R^{6a} and R^{6b} is hydrogen and the other is methyl, and R^7 is hydrogen or C_1-C_6 linear, branched, or cyclic alkyl.

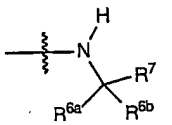


Non-limiting examples of this iteration include isopropylamino, and *sec*-butylamino.

iii) A third iteration of this aspect includes units wherein both R^{6a} and R^{6b} are each hydrogen and R^7 is substituted C_1-C_6 linear, branched, or cyclic alkyl. Non-limiting examples of this iteration include 2-methoxyethylamino, and 2-methoxy-2-methyl-propylamino.

iv) A fourth iteration of this aspect includes units wherein one unit of R^{6a} and R^{6b} is hydrogen and the other is methyl, and R^7 is substituted C_1-C_6 linear, branched, or cyclic alkyl. Non-limiting examples of this iteration include 1-methyl-2-methoxy-ethylamino, and 1,2-dimethyl-2-methoxyethylamino.

C) R units encompassing racemic amino groups wherein R^{5a} is hydrogen, R^{6a} or R^{8b} is hydrogen or $-CO_2R^8$; R^8 is hydrogen or methyl; and R^7 is hydrogen or substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl, substituted or unsubstituted heterocyclic, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; said units having the formula:

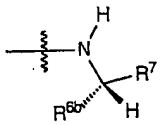


i) A first iteration of this aspect includes units which are derived from alkyl unit comprising amino acids and amino acid methyl esters. Non-limiting examples of this iteration include carboxymethylamino (from glycine), (carboxymethyl)-

methylamino (from glycine methylester), and 1-(carboxy)ethylamino (from alanine).

ii) A second iteration of this aspect includes units which are derived from substituted or unsubstituted aryl unit comprising amino acids and amino acid methyl esters. Non-limiting examples include (α)-carboxybenzylamino (from phenylalanine) and 1-carboxy-2-(4-hydroxyphenyl)ethylamino (from tyrosine).

D) R units encompassing chiral amino groups wherein R^{5a} is hydrogen, R^{6a} is hydrogen, R^{6b} is C_1-C_4 alkyl, and R^7 is substituted or unsubstituted aryl or heteroaryl, said units having the formula:

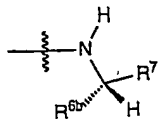


with the indicated stereochemistry.

i) A first iteration of this aspect includes units wherein R^{6b} is methyl, R^7 is aryl or substituted aryl. Non-limiting examples of this iteration include (*S*)-(α)-methylbenzylamino, (*S*)-1-methyl-1-(4-fluorophenyl)methylamino, (*S*)-1-methyl-1-(2-aminophenyl)methylamino , (*S*)-1-methyl-1-(2-methylphenyl)methylamino , (*S*)-1-methyl-1-(4-methylphenyl)methylamino, and (*S*)-1-methyl-1-(4-methoxyphenyl)-methylamino.

ii) A second iteration of this aspect includes units wherein R^{6b} is ethyl or hydroxyethyl, R^7 is aryl or substituted aryl. Non-limiting examples of this iteration include (*S*)-(α)-ethylbenzylamino, (*S*)-1-(4-fluorophenyl)ethylamino, (*S*)-1-(2-aminophenyl)-ethylamino , (*S*)-1-ethyl-1-(2-methylphenyl)amino , (*S*)-1-(4-methylphenyl)-ethylamino, (*S*)-1-(4-methoxyphenyl)ethylamino, and (*S*)-1-(4-fluorophenyl)-2-hydroxyethylamino.

E) R units encompassing chiral amino groups wherein R^{5a} is hydrogen, R^{6a} is hydrogen, R^{6b} is C_1-C_4 alkyl, and R^7 is substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl, said units having the formula:



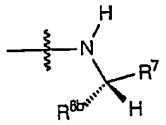
with the indicated stereochemistry.

i) A first iteration of this aspect includes units wherein R^{6b} is methyl and R^7 is C_1-C_6 linear, branched, or cyclic alkyl. Non-limiting examples of this iteration include (*S*)-1-methylpropylamino, (*S*)-1-methyl-1-methoxyethylamino, (*S*)-1-methyl-2-(*S*)-

methoxypropylamino, (*S*)-1,2-dimethyl-2-hydroxypropylamino, and (*S*)-1,2-methyl-2-methoxypropylamino.

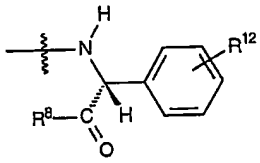
ii) A second iteration of this aspect includes units wherein R^{6b} is C_2-C_4 alkyl and R^7 is C_1-C_6 linear, branched, or cyclic alkyl. Non-limiting examples of this iteration include (*S*)-1-ethylpropylamino, (*S*)-1-ethyl-1-methoxyethylamino, (*S*)-1-ethyl-2-(*S*)-methoxypropylamino, and (*S*)-1-ethyl-2-methyl-2-methoxypropylamino.

F) R units encompassing chiral amino groups wherein R^{5a} is hydrogen, R^{6a} or R^{6b} is hydrogen or $-CO_2R^8$; R^8 is hydrogen or methyl; and R^7 is hydrogen or substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl, substituted or unsubstituted heterocyclic, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; said units having the formula:



with the indicated stereochemistry.

i) A first iteration of this aspect includes R units which are derived from aryl unit comprising amino acids and amino acid methyl esters, said units having the formula:



wherein R^8 is hydrogen or methyl. Non-limiting examples include (*S*)-(α)-carboxybenzylamino (R unit derived from L-phenylglycine).

ii) A second iteration of this aspect includes units which are derived from substituted or unsubstituted alkyl unit comprising amino acids and amino acid methyl esters. Non-limiting examples of this iteration include 1-(*S*)-(carboxy)ethylamino (from L-alanine).

R^1 is substituted phenyl. The units may be substituted by any "substituent" group described herein above.

The first aspect of R^1 units relates to halogen substituted phenyl, for example, 4-fluorophenyl 2,4-difluorophenyl, 4-chlorophenyl, and the like. A second aspect relates to methyl substituted phenyl, for example, 3-methylphenyl and 4-methylphenyl. A third aspect relates to trifluoromethyl ring substituents, non-limiting examples of which include 3-trifluoromethylphenyl.

Each R^2 and R^3 unit is independently selected from:

a) hydrogen; and

b) substituted or unsubstituted C_1-C_{10} hydrocarbyl selected from:

i) C_1-C_{10} linear, branched or cyclic alkyl;

ii) C_1-C_{10} aryl;

iii) C_1-C_{10} heterocyclic;

iv) C_1-C_{10} heteroaryl.

Among the definitions of cyclic alkyl, aryl, heterocyclic, and heteroaryl as it relates to the R^2 and R^3 units of the present invention, are included rings formed from functional groups and rings attached to the 1,2-dihydropyrazol-3-one ring scaffold by a tether. The tether is typically one or more alkylene units. These units include:

a) $-(CH_2)_jR^9$;

b) $-(CH_2)_jNR^{10a}R^{10b}$;

c) $-(CH_2)_jCON(R^{11})_2$;

d) $-(CH_2)_jOCON(R^{11})_2$;

e) and mixtures thereof;

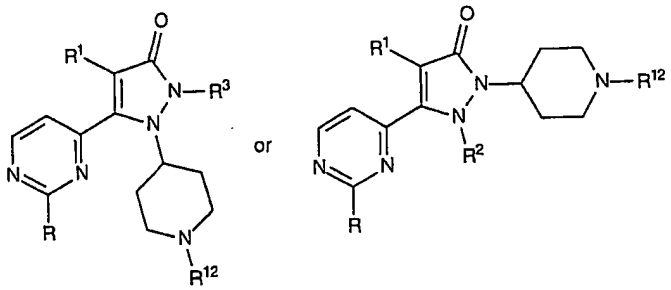
wherein R^9 is a cyclic ether unit, *inter alia*, pyranyl and furanyl; R^{10a} and R^{10b} or two R^{11} units are taken together to form a heterocyclic or heteroaryl unit comprising from 3 to 7 atoms; j is an index from 0 to 5, n is an index from 0 to 5.

The first aspect of R^2 and R^3 relates to 1,2-dihydropyrazol-3-one ring scaffolds wherein both R^2 and R^3 are each hydrogen. One iteration includes the generic compounds encompassed by 4-(R^1)-5-[2-R-pyrimidin-4-yl]-1,2-dihydro-pyrazol-3-one.

The second aspect of R^2 and R^3 relates to 1,2-dihydropyrazol-3-one ring scaffolds wherein R^2 is a substituted or unsubstituted heterocyclic ring and R^3 is a substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl unit. One iteration includes the generic compounds encompassed by 1-(piperidin-4-yl)-2-methyl-4-(R^1)-5-[2-R-pyrimidin-4-yl]-1,2-dihydro-pyrazol-3-one.

The third aspect of R^2 and R^3 relates to 1,2-dihydropyrazol-3-one ring scaffolds wherein R^2 is a substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl unit and R^3 is a substituted or unsubstituted heterocyclic ring. One iteration includes the generic compounds encompassed by 1-methyl-2-(piperidin-4-yl)-4-(R^1)-5-[2-R-pyrimidin-4-yl]-1,2-dihydro-pyrazol-3-one.

Non-limiting examples of the second and third aspects of R^2 and R^3 units encompass the substituted and unsubstituted rings, *inter alia*, scaffolds having the formula:



and R^{12} is $-[C(R^{13})_2]_pC(O)_2R^{13}$, non-limiting examples of which include $-(CH_2)CO_2H$, $-(CH_2)CO_2CH_3$, $-[CH(CH_3)]CO_2H$, $-[CH(CH_3)]CO_2CH_3$, $-[C(CH_3)_2]CO_2H$, $-[C(CH_3)_2]CO_2CH_3$, or the water soluble salts of the acids.

The fourth aspect of R^2 and R^3 relates to 1,2-dihydropyrazol-3-one ring scaffolds wherein R^2 and R^3 are each independently C_1-C_6 alkyl. One iteration of this aspect relates to rings wherein R^2 and R^3 units are the same, *inter alia*, the generic compounds 1,2-dimethyl-4-(R^1)-5-[2-R-pyrimidin-4-yl]-1,2-dihydro-pyrazol-3-one and 1,2-diethyl-4-(R^1)-5-[2-R-pyrimidin-4-yl]-1,2-dihydro-pyrazol-3-one.

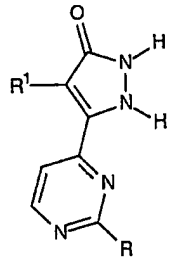
However, other non-exemplified aspects include compounds, *inter alia*, under the generic formulae 1-substituted aryl-2-(piperidin-4-yl)-4-(R^1)-5-[2-R-pyrimidin-4-yl]-1,2-dihydro-pyrazol-3-one, 1-(morpholin-4-yl)-2-(heteroaryl)-4-(R^1)-5-[2-R-pyrimidin-4-yl]-1,2-dihydro-pyrazol-3-one, and 1-heteroaryl-2-substitued aryl-4-(R^1)-5-[2-R-pyrimidin-4-yl]-1,2-dihydro-pyrazol-3-one.

Selection of R^2 and R^3 units and combinations thereof directly relate to the Categories described herein below. For example, compounds wherein both R^2 and R^3 are each methyl, ethyl, or other lower alkyl, relates to Category IV analogs.

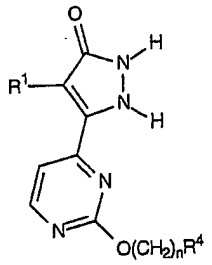
The analogs (compounds) of the present invention are arranged in several categories to assist the formulator in applying a rational synthetic strategy for the preparation of analogs which are not expressly exampled herein. The arrangement into categories does not imply increased or decreased efficacy for any of the compositions of matter described herein.

The analogs (compounds) of the present invention are conveniently obtained in the salt form, for example, the trifluoroacetate salt, especially after removal of protecting groups with trifluoroacetic acid as the last step in their preparation. However, the formulator may neutralize the analogs, or convert them to another salt form without change to the efficacy of the parent compounds. Also, the formulator, if convenient or practicable, will prepare a pro-drug which will release the active compound (analog) upon uptake by the host. All of these variations are encompassed within the present invention.

The first category of inflammatory cytokine release inhibiting compounds according to the present invention are 4-R^1-substituted-5-(2-R-substituted-pyrimidin-4-yl)-1,2-dihydropyrazol-3-ones having the general scaffold with the formula:



wherein the first aspect of Category I has the formula:



R^1 and R^4 are described herein below in Table I. The index n can be 0 or 1.

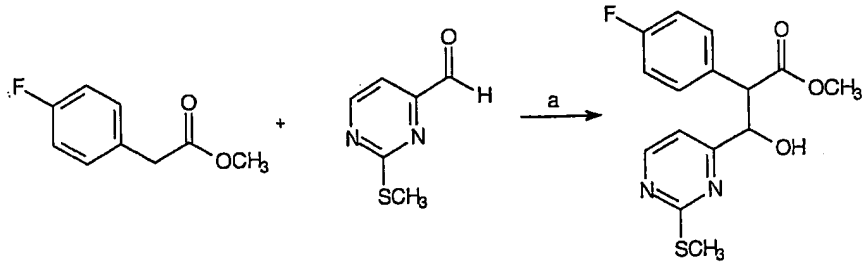
TABLE I

No.	R^1	R^4
1	4-fluorophenyl	phenyl
2	4-fluorophenyl	2-fluorophenyl
3	4-fluorophenyl	3-fluorophenyl
4	4-fluorophenyl	4-fluorophenyl
5	4-fluorophenyl	2,6-difluorophenyl
6	4-fluorophenyl	2-cyanophenyl
7	4-fluorophenyl	3-cyanophenyl
8	4-fluorophenyl	2-trifluoromethylphenyl
9	4-fluorophenyl	4-trifluoromethylphenyl
10	4-fluorophenyl	*N*-methylpiperadin-4-yl
11	4-fluorophenyl	4-methylphenyl
12	4-fluorophenyl	2,4-dimethylphenyl
13	4-fluorophenyl	3-*N*-acetylaminophenyl
14	4-fluorophenyl	pyran-4-yl
15	4-fluorophenyl	4-methoxyphenyl
16	4-fluorophenyl	3-benzo[1,3]dioxol-5-yl
17	2,4-difluorophenyl	phenyl
18	2,4-difluorophenyl	2-fluorophenyl
19	2,4-difluorophenyl	3-fluorophenyl

20	2,4-difluorophenyl	4-fluorophenyl
21	2,4-difluorophenyl	2,6-difluorophenyl
22	2,4-difluorophenyl	2-cyanophenyl
23	2,4-difluorophenyl	3-cyanophenyl
24	2,4-difluorophenyl	2-trifluoromethylphenyl
25	2,4-difluorophenyl	4-trifluoromethylphenyl
26	2,4-difluorophenyl	*N*-methylpiperadin-4-yl
27	2,4-difluorophenyl	4-methylphenyl
28	2,4-difluorophenyl	2,4-dimethylphenyl
29	2,4-difluorophenyl	3-N-acetylaminophenyl
30	2,4-difluorophenyl	pyran-4-yl
31	2,4-difluorophenyl	4-methoxyphenyl
32	2,4-difluorophenyl	3-benzo[1,3]dioxol-5-yl
33	3-trifluoromethylphenyl	phenyl
34	3-trifluoromethylphenyl	2-fluorophenyl
35	3-trifluoromethylphenyl	3-fluorophenyl
36	3-trifluoromethylphenyl	4-fluorophenyl
37	3-trifluoromethylphenyl	2,6-difluorophenyl
38	3-trifluoromethylphenyl	2-cyanophenyl
39	3-trifluoromethylphenyl	3-cyanophenyl
40	3-trifluoromethylphenyl	2-trifluoromethylphenyl
41	3-trifluoromethylphenyl	4-trifluoromethylphenyl
42	3-trifluoromethylphenyl	*N*-methylpiperadin-4-yl
43	3-trifluoromethylphenyl	4-methylphenyl
44	3-trifluoromethylphenyl	2,4-dimethylphenyl
45	3-trifluoromethylphenyl	3-N-acetylaminophenyl
46	3-trifluoromethylphenyl	pyran-4-yl
47	3-trifluoromethylphenyl	4-methoxyphenyl
48	3-trifluoromethylphenyl	3-benzo[1,3]dioxol-5-yl

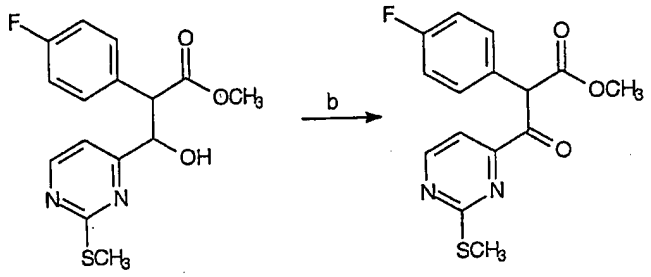
The analogs 1-48 are non-limiting examples of analogs which comprise the first aspect of Category I. The analogs of the first aspect of Category I can be suitably prepared by the procedure outlined herein below. In the following example, R^1 is 4-fluorophenyl, however, the formulator may suitably substitute any starting material compatible with this procedure, *inter alia*, methyl phenylacetate, methyl 4-chlorophenylacetate, and methyl 3-(trifluoromethyl)phenylacetate.

Scheme I: Preparation of First Aspect of Category I



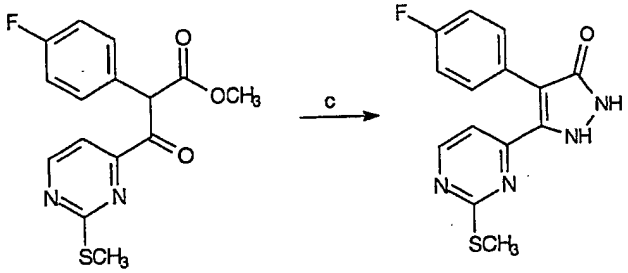
1 2

Reagents and conditions: (a) LDA, THF; -78 °C, 1 hr.



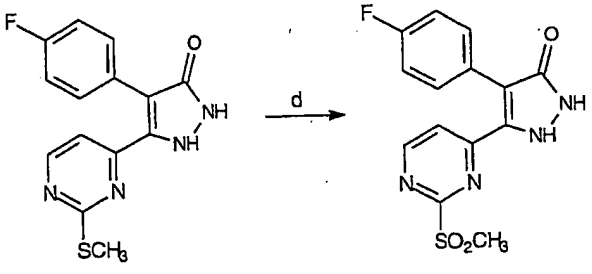
2 3

Reagents and conditions: (b) CrO_3, CH_2Cl_2; rt 16 hr.



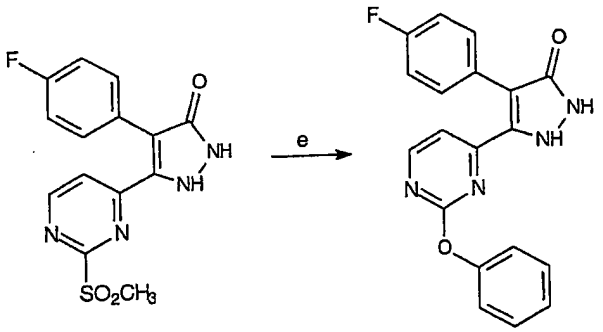
3 4

Reagents and conditions: (c) $H_2NNHC(O)NH_2$, pyridine; 90 °C, 12 hr.



4 5

Reagents and conditions: (d) Oxone®, MeOH/THF/H_2O; rt, 1 hr.



5 6

Reagents and conditions: (e) phenol, NaH, THF, 1.5 hr rt.

EXAMPLE 1

4-(4-Fluorophenyl)-5-[2-(phenoxy)pyrimidin-4-yl]-1,2dihydropyrazol-3-one (6)

The following is a procedure for the preparation of 2-methylsulfanyl-pyrimidine-4-carbaldehyde, 1, adapted from the procedure of H. Bredereck et al., *Chem. Ber.*, **97**, pp 3407-3417 (1964) included herein by reference.

To a 12 L 3-neck flask under inert atmosphere is charged N,N-dimethyl-formamide dimethyl acetyl (801 g) and pyruvic aldehyde dimethyl acetal (779 g). The mixture is heated to reflux for 18 hours during which time the temperature decreases from about 109 °C to about 80 °C. The solution is cooled and methanol (4 L) is added to dissolve the crude residue. The solution is then cooled to 20 °C and thiourea (892 g, 11.7 mol) is added. After allowing the mixture to stir about 15 minutes, sodium methoxide (741 g, 13.7 mol) is added in 4 equal portions over 1 hour while maintaining the solution temperature in the range of 18 – 28 °C. The mixture is stirred for 5 hours at room temperature, cooled to 20 °C, then methyl iodide (2 kg) is added over 1.25 hours while maintaining the reaction temperature in the range of 17 – 29 °C. Stirring is continued for 18 hours at room temperature. The methanol and unreacted methyl iodide is removed by heating the solution at 35 °C @ 40 torr to produce about 4.46 kg of a dark residue which is partitioned between 14 L of water and 5 L of ethyl acetate. The water fraction is extracted a second time with ethyl acetate, the organic layers combined and concentrated *in vacuo* too afford 685 g of an oil which is purified over silica to 522 g of 4-dimethoxymethyl-2-methylsulfanyl-pyrimidine.

The dimethyl acetal obtained above is then hydrolyzed to the free aldehyde by heating to 60 °C for 3 hours in 1 M HCl. Workup for neutral using ethyl acetate to extract the product affords 347 g crude product which is purified over silica to afford 2-methylsulfanyl-pyrimidine-4-carbaldehyde, 1.

Preparation of 2-(4-fluorophenyl)-3-(2-methylsulfanyl-pyrimidin-4-yl)-3-hydroxypropionic acid methyl ester (2): To a cold (-78 °C) solution of lithium diisopropylamide (21.4 mL of 2M solution in THF, 42.8 mmol) in THF (70 mL) is added dropwise a solution of methyl 4-fluorophenyl-acetate (6.0 g, 35.7 mmol) in THF (30 mL). The solution is stirred for 1 hour at –78 °C after which a solution of 2-methylsulfanyl-pyrimidine-4-carbaldehyde, **1**, (6.0 g, 39.3 mmol) in THF (30 mL) is added dropwise to the reaction mixture. Stirring is continued for 45 minutes at –78 °C then the reaction is quenched by pouring the reaction solution into aqueous saturated NH_4Cl. The aqueous phase is extracted with ethyl acetate. The organic phases combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue is purified over silica (33%EtOAc/hexanes) to afford 8.7 g (76%) of the desired product as a mixture (1:1) of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (dd, J = 4.5, 1.5 Hz, 2H), 7.21-7.15 (m, 4H), 6.99 (t, J = 9.0 Hz, 2H), 5.38 (d, J = 5.4 Hz, 1H), 3.83 (d, J = 5.4 Hz, 1H), 3.67 (s, 3H); ESI/MS: 276.1 (M+H).

Preparation of 2-(4-fluorophenyl)-3-(2-methylsulfanyl-pyrimidin-4-yl)-3-oxo-propionic acid methyl ester (3): To a suspension of CrO_3 in CH_2Cl_2 (300 mL) is added pyridine. The mixture is stirred vigorously for 1 hour at room temp. A solution of the crude 2-(4-fluorophenyl)-3-(2-methylsulfanyl-pyrimidin-4-yl)-3-hydroxypropionic acid methyl ester, **2**, prepared above in CH_2Cl_2 (50 mL) is added dropwise to the chromium suspension. The reaction mixture is stirred at room temperature for 16 hours, diluted with ether (1 L) and filtered through a pad of Celite. The filtrate is concentrated *in vacuo* and the resulting residue is purified over silica (25% EtOAc/hexanes) to afford 3.7 g (43% yield) of the desired product as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (d, J = 4.8 Hz, 1H), 7.59 (d, J = 4.8 Hz, 1H), 7.40 (dd, J = 8.7, 5.4 Hz, 2H), 7.10 (t, J = 8.7 Hz, 2H), 5.97 (s, 1H), 3.79 (s, 3H), 2.63 (s, 3H); ESI/MS: 321.0 (M+H)..

Preparation of 4-(4-fluorophenyl)-5-(2-methylsulfanylpyrimidin-4-yl)-1,2-dihydro-pyrazol-3-one (4): A solution of 2-(4-fluorophenyl)-3-(2-methylsulfanyl-pyrimidin-4-yl)-3-oxo-propionic acid methyl ester, **3**, (1 g, 3.7 mmol), semicarbazide HCl (0.653 g, 5.8 mmol) and pyridine (10 mL) is heated at 90 °C for 12 hours. The solution is then concentrated *in vacuo* to afford a semi-solid residue which is taken up in methanol and the resulting solid removed by filtration. The filtrate is concentrated *in vacuo* to afford the desired compound as a white solid, which is used without further purification.

Preparation of 4-(4-fluorophenyl)-5-(2-methanesulfonylpyrimidin-4-yl)-1,2-dihydro-pyrazol-3-one (5): To a solution of 4-(4-fluorophenyl)-5-(2-methylsulfanylpyrimidin-4-yl)-1,2-dihydro-pyrazol-3-one, **4**, (3.0 g, 10 mmol) in THF:methanol (100 mL of a 1:1 mixture) is added

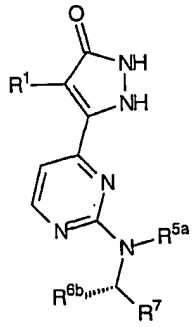
dropwise a solution of Oxone® (potassium peroxymonosulfate) (24.6 g, 40 mmol) in water (100 mL). The reaction is stirred 1 hour at room temperature, diluted with aqueous $NaHCO_3$ and extract three times with ethyl acetate. The organic layers are combined, dried, and concentrated *in vacuo* to afford the crude desired product which is used without further purification.

Preparation of 4-(4-Fluorophenyl)-5-[2-(phenoxy)pyrimidin-4-yl]-1,2dihydropyrazol-3-one (6): To a solution of phenol (0.66 g, 7.08 mmol) in THF (5 mL) is added NaH (0.24 g, 5.91 mmol) followed by a solution of the crude 4-(4-fluorophenyl)-5-(2-methanesulfonylpyrimidin-4-yl)-1,2-dihydro-pyrazol-3-one, 5, prepared herein above (0.22 g, 0.67 mmol) in THF (2 mL). The reaction mixture is stirred for 1.5 hours at room temperature, diluted with aqueous $NaHCO_3$ and extracted with twice with ethyl acetate. The organic layers are combined, dried over $MgSO_4$, and concentrated *in vacuo* to afford the crude product which is purified over silica (100% EtOAc, followed by 10% MeOH/EtOAc) to provide the desired product as a yellow solid.

The following are non-limiting examples of compounds from the first aspect of Category I can be prepared by the procedure described herein above.

5-(2-Phenoxypyrimidin-4-yl)-4-(4-fluorophenyl)-1,2-dihydropyrazol-3-one;
5-[2-(2-Hydroxyphenoxy)pyrimidin-4-yl]-4-(4-fluorophenyl)-1,2-dihydropyrazol-3-one;
5-[2-(4-Hydroxyphenoxy)pyrimidin-4-yl]-4-(4-fluorophenyl)-1,2-dihydropyrazol-3-one;
5-[2-(2-*N*-Acetylphenoxy)pyrimidin-4-yl]-4-(4-fluorophenyl)-1,2-dihydropyrazol-3-one;
5-[2-(3-*N*-Acetylphenoxy)pyrimidin-4-yl]-4-(4-fluorophenyl)-1,2-dihydropyrazol-3-one;
5-[2-(2-Cyanophenoxy)pyrimidin-4-yl]-4-(4-fluorophenyl)-1,2-dihydropyrazol-3-one;
5-[2-(2-Fluorophenoxy)pyrimidin-4-yl]-4-(4-fluorophenyl)-1,2-dihydropyrazol-3-one;
5-[2-(4-Fluorophenoxy)pyrimidin-4-yl]-4-(4-fluorophenyl)-1,2-dihydropyrazol-3-one;
5-(2-Benzoxypyrimidin-4-yl)-4-(4-fluorophenyl)-1,2-dihydropyrazol-3-one;
5-[2-(*S*)-(α-methylbenzoxy)pyrimidin-4-yl]-4-(4-fluorophenyl)-1,2-dihydropyrazol-3-one;
5-[2-(*R*)-(α-methylbenzoxy)pyrimidin-4-yl]-4-(4-fluorophenyl)-1,2-dihydropyrazol-3-one;

A second aspect of the Category I inflammatory cytokine release inhibiting compounds according to the present invention have the general scaffold having the formula:



wherein R^1, R^{5a}, R^{6b}, and R^7 are described herein below in Table II. The stereochemistry indicated above is present for the analogs of Table II when R^{6b} or R^7 is not hydrogen. However, analogs having the opposite stereochemistry are equally encompassed within the scope of the second aspect of Category II.

TABLE II

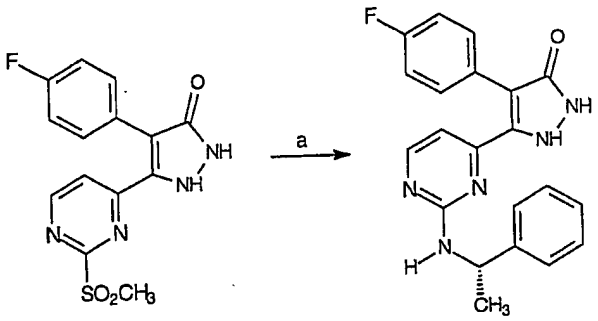
No.	R^1	R^{5a}	R^{6b}	R^7
49	4-fluorophenyl	H	H	phenyl
50	4-fluorophenyl	H	H	4-fluorophenyl
51	4-fluorophenyl	H	H	2-aminophenyl
52	4-fluorophenyl	H	H	2-methylphenyl
53	4-fluorophenyl	H	H	4-methylphenyl
54	4-fluorophenyl	H	H	4-methoxyphenyl
55	4-fluorophenyl	H	H	4-(propanesulfonyl)phenyl
56	4-fluorophenyl	H	H	3-benzo[1,3]dioxol-5-yl
57	4-fluorophenyl	H	H	pyridin-2-yl
58	4-fluorophenyl	H	H	pyridin-3-yl
59	4-fluorophenyl	H	methyl	phenyl
60	4-fluorophenyl	H	methyl	4-fluorophenyl
61	4-fluorophenyl	H	methyl	2-aminophenyl
62	4-fluorophenyl	H	methyl	2-methylphenyl
63	4-fluorophenyl	H	methyl	4-methylphenyl
64	4-fluorophenyl	H	methyl	4-methoxyphenyl
65	4-fluorophenyl	H	methyl	4-(propanesulfonyl)phenyl
66	4-fluorophenyl	H	methyl	3-benzo[1,3]dioxol-5-yl
67	4-fluorophenyl	H	methyl	pyridin-2-yl
68	4-fluorophenyl	H	methyl	pyridin-3-yl
69	4-fluorophenyl	H	H	H
70	4-fluorophenyl	H	H	methyl

71	4-fluorophenyl	H	H	ethyl
72	4-fluorophenyl	H	H	vinyl
73	4-fluorophenyl	H	H	cyclopropyl
74	4-fluorophenyl	H	H	cyclohexyl
75	4-fluorophenyl	H	H	methoxymethyl
76	4-fluorophenyl	H	H	methoxyethyl
77	4-fluorophenyl	H	H	1-hydroxy-1-methylethyl
78	4-fluorophenyl	H	H	$-CO_2H$
79	4-fluorophenyl	H	methyl	H
80	4-fluorophenyl	H	methyl	methyl
81	4-fluorophenyl	H	methyl	ethyl
82	4-fluorophenyl	H	methyl	vinyl
83	4-fluorophenyl	H	methyl	cyclopropyl
84	4-fluorophenyl	H	methyl	cyclohexyl
85	4-fluorophenyl	H	methyl	methoxymethyl
86	4-fluorophenyl	H	methyl	methoxyethyl
87	4-fluorophenyl	H	methyl	1-hydroxy-1-methylethyl
88	4-fluorophenyl	H	methyl	$-CO_2H$
89	3-trifluoromethylphenyl	H	methyl	phenyl
90	3-trifluoromethylphenyl	H	methyl	4-fluorophenyl
91	3-trifluoromethylphenyl	H	methyl	2-aminophenyl
92	3-trifluoromethylphenyl	H	methyl	2-methylphenyl
93	3-trifluoromethylphenyl	H	methyl	4-methylphenyl
94	3-trifluoromethylphenyl	H	methyl	4-methoxyphenyl
95	3-trifluoromethylphenyl	H	methyl	4-(propanesulfonyl)phenyl
96	3-trifluoromethylphenyl	H	methyl	3-benzo[1,3]dioxol-5-yl
97	3-trifluoromethylphenyl	H	methyl	pyridin-2-yl
98	3-trifluoromethylphenyl	H	methyl	pyridin-3-yl
99	3-trifluoromethylphenyl	H	methyl	H
100	3-trifluoromethylphenyl	H	methyl	methyl
101	3-trifluoromethylphenyl	H	methyl	ethyl
102	3-trifluoromethylphenyl	H	methyl	vinyl
103	3-trifluoromethylphenyl	H	methyl	cyclopropyl
104	3-trifluoromethylphenyl	H	methyl	cyclohexyl
105	3-trifluoromethylphenyl	H	methyl	methoxymethyl
106	3-trifluoromethylphenyl	H	methyl	methoxyethyl

107	3-trifluoromethylphenyl	H	methyl	1-hydroxy-1-methylethyl
108	3-trifluoromethylphenyl	H	methyl	$-CO_2H$

Utilizing intermediates such as compound **5**, as a convenient starting point the analogs 49-108 and others encompassed within the description of this category can be suitably prepared by the procedure outlined herein below. In the following example, R^1 is 4-fluorophenyl, however, the formulator may suitably substitute any starting material compatible with this procedure, *inter alia*, methyl phenylacetate, methyl 4-chlorophenyl-acetate, and methyl 3-(trifluoromethyl)phenyl acetate.

Scheme II: Preparation of Second Aspect of Category I



5 **7**

Reagents and conditions: (a) (S)-(α)-methylbenzylamine, toluene, 140 °C, 12 hr.

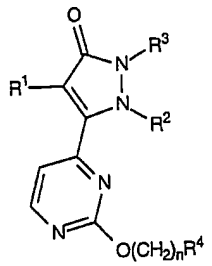
EXAMPLE 2

2-(4-Fluorophenyl)-3-[2-(*S*)-(1-phenylethylamino)pyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (7)

Preparation of 2-(4-fluorophenyl)-3-[2-(*S*)-(1-phenylethylamino)pyrimidin-4-yl]-6,7-dihydro-5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (7): Crude 2-(4-fluorophenyl)-3-(2-methanesulfonyl-pyrimidin-4-yl)-6,7-dihydro-5H-pyrazolo[1,2-a]pyrazol-1-one, **5**, prepared herein above (0.86 g, 2.3 mmol) and (*S*)-(-)-α-methyl-benzyl amine (10.5 mL, 81.6 mmol) is dissolved in toluene (18 mL). The resulting mixture is heated to 140 °C for 12 hours, cooled to room temperature and the solvent removed *in vacuo*. The resulting residue is purified over silica (1:1 EtOAc/hexanes) to afford the desired product which to analog 59 from Table II. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J = 5.1 Hz, 1H), 7.42-7.34 (m, 7H), 7.04 (ddd, J = 9.0, 6.9, 2.1 Hz, 2H), 6.39 (d, J = 5.1 Hz, 1H),

5.68 (bd s, 1H), 5.10 (m, 1H), 3.97 (dt, J = 7.5, 7.5, 7.5 Hz, 2H), 2.45 (bd s, 2H), 1.67 (m, 2H), 1.60 (d, J = 7.5 Hz, 3H); HRMS calcd for $C_{24}H_{22}FN_5O$ $(M + H)^+$ 416.1887; found 416.1897.

The second category of inflammatory cytokine release inhibiting compounds according to the present invention are 4-R^1-substituted-5-(2-R-substituted-pyrimidin-4-yl)-1,2-dihydropyrazol-3-ones having the general scaffold with the formula:



wherein the first aspect of Category II comprises R^2 comprising a substituted or unsubstituted ring, R^3 comprising a C_1-C_4 linear, branched, or cyclic alkyl unit, and the index n is 0, as defined in Table III herein below.

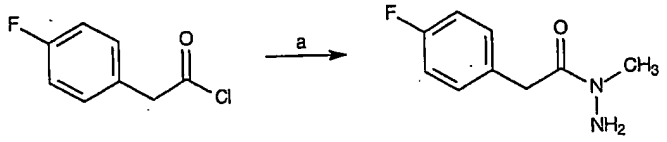
TABLE III

No.	R^1	R^2	R^3	R^4
109	4-fluorophenyl	piperidin-4-yl	methyl	phenyl
110	4-fluorophenyl	piperidin-4-yl	methyl	2-hydroxyphenyl
111	4-fluorophenyl	piperidin-4-yl	methyl	4-hydroxyphenyl
112	4-fluorophenyl	piperidin-4-yl	methyl	2-*N*-acetylaminophenyl
113	4-fluorophenyl	piperidin-4-yl	methyl	3-*N*-acetylaminophenyl
114	4-fluorophenyl	piperidin-4-yl	methyl	2-cyanophenyl
115	4-fluorophenyl	piperidin-4-yl	methyl	4-fluorophenyl
116	4-fluorophenyl	piperidin-4-yl	methyl	benzyl
117	4-fluorophenyl	piperidin-4-yl	methyl	(S)-α-methylbenzyl
118	4-fluorophenyl	piperidin-4-yl	methyl	(R)-α-methylbenzyl
119	4-fluorophenyl	*N*-methylpiperidin-4-yl	methyl	phenyl
120	4-fluorophenyl	*N*-methylpiperidin-4-yl	methyl	2-hydroxyphenyl
121	4-fluorophenyl	*N*-methylpiperidin-4-yl	methyl	4-hydroxyphenyl
122	4-fluorophenyl	*N*-methylpiperidin-4-yl	methyl	2-*N*-acetylaminophenyl
123	4-fluorophenyl	*N*-methylpiperidin-4-yl	methyl	3-*N*-acetylaminophenyl
124	4-fluorophenyl	*N*-methylpiperidin-4-yl	methyl	2-cyanophenyl
125	4-fluorophenyl	*N*-methylpiperidin-4-yl	methyl	4-fluorophenyl

126	4-fluorophenyl	*N*-methylpiperidin-4-yl	methyl	benzyl
127	4-fluorophenyl	*N*-methylpiperidin-4-yl	methyl	(S)-α-methylbenzyl
128	4-fluorophenyl	*N*-methylpiperidin-4-yl	methyl	(R)-α-methylbenzyl
129	4-fluorophenyl	morpholin-4-yl	methyl	phenyl
130	4-fluorophenyl	morpholin-4-yl	methyl	2-hydroxyphenyl
131	4-fluorophenyl	morpholin-4-yl	methyl	4-hydroxyphenyl
132	4-fluorophenyl	morpholin-4-yl	methyl	2-*N*-acetylaminophenyl
133	4-fluorophenyl	morpholin-4-yl	methyl	3-*N*-acetylaminophenyl
134	4-fluorophenyl	morpholin-4-yl	methyl	2-cyanophenyl
135	4-fluorophenyl	morpholin-4-yl	methyl	4-fluorophenyl
136	4-fluorophenyl	morpholin-4-yl	methyl	benzyl
137	4-fluorophenyl	morpholin-4-yl	methyl	(S)-α-methylbenzyl
138	4-fluorophenyl	morpholin-4-yl	methyl	(R)-α-methylbenzyl
139	4-fluorophenyl	*N*-acetylpiperidin-4-yl	methyl	phenyl
140	4-fluorophenyl	*N*-acetylpiperidin-4-yl	methyl	2-hydroxyphenyl
141	4-fluorophenyl	*N*-acetylpiperidin-4-yl	methyl	4-hydroxyphenyl
142	4-fluorophenyl	*N*-acetylpiperidin-4-yl	methyl	2-*N*-acetylaminophenyl
143	4-fluorophenyl	*N*-acetylpiperidin-4-yl	methyl	3-*N*-acetylaminophenyl
144	4-fluorophenyl	*N*-acetylpiperidin-4-yl	methyl	2-cyanophenyl
145	4-fluorophenyl	*N*-acetylpiperidin-4-yl	methyl	4-fluorophenyl
146	4-fluorophenyl	*N*-acetylpiperidin-4-yl	methyl	benzyl
147	4-fluorophenyl	*N*-acetylpiperidin-4-yl	methyl	(S)-α-methylbenzyl
148	4-fluorophenyl	*N*-acetylpiperidin-4-yl	methyl	(R)-α-methylbenzyl

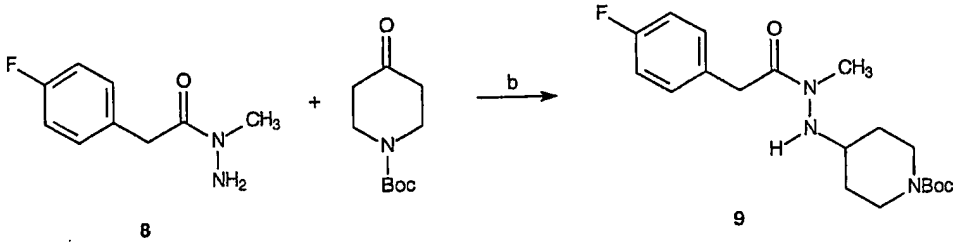
The following is an example of the preparation of compounds encompassed within the first aspect of Category II analogs according to the present invention.

Scheme III: Preparation of First Aspect of Category II



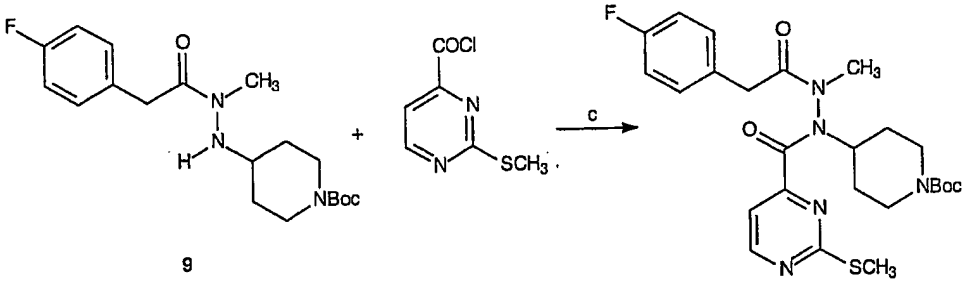
8

Reagents and conditions: (a) H_2NNHCH_3, CH_2Cl_2; -78 °C to rt, 2 hr.



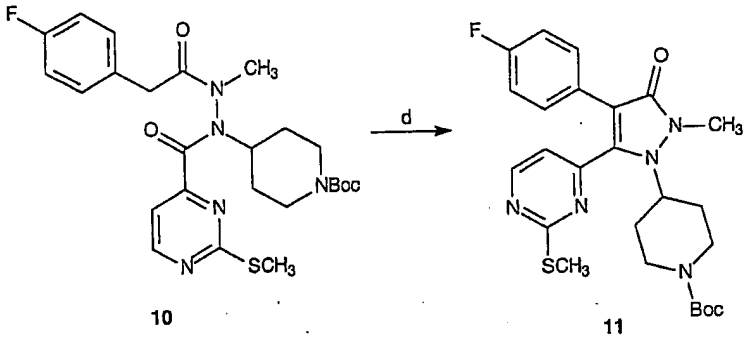
8 9

Reagents and conditions: (b) i) reflux 0.5 hr; il) $NaCNBH_3$, HCl, EtOH; rt, 3 hr.



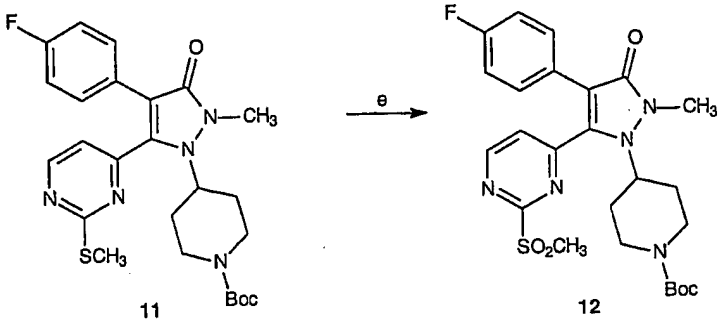
9 10

Reagents and conditions: (c) pyridine; rt, 2 hr.



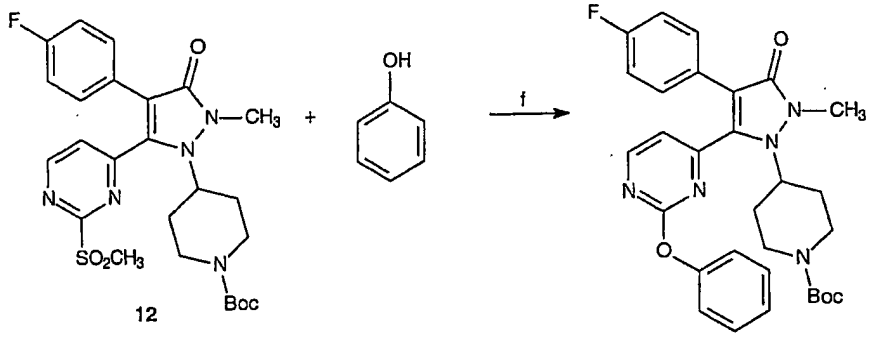
10 11

Reagents and conditions: (d) NaH, DMF; 0 °C, 1 hr.



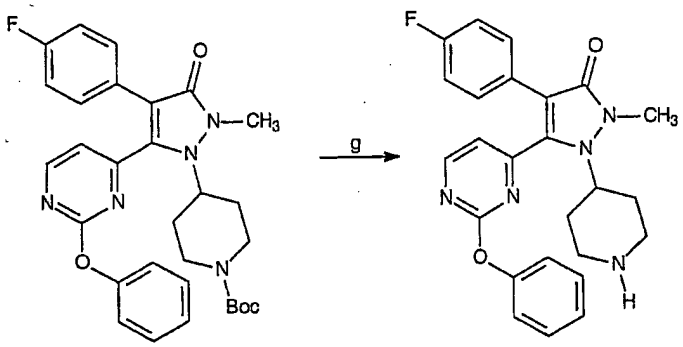
11 12

Reagents and conditions: (e) m-CPBA, $CHCl_3$; 0 °C, 5 min.



12 13

Reagents and conditions: (f) NaH, THF; rt, 14 hr.



13 14

Reagents and conditions: (g) TFA, CH_2Cl_2; rt, 30 min.

EXAMPLE 3

4-(4-Fluorophenyl)-2-methyl-5-(2-phenoxy-pyrimidin-4-yl)-1-piperidin-4-yl-1,2-dihydro-pyrazol-3-one (14)

Preparation of (4-fluorophenyl)-acetic acid N-methyl-hydrazide (8). To a –78°C stirred solution of methyl hydrazine (11 mL, 208.5 mmol) in CH_2Cl_2 (100 mL) is added dropwise a solution of commercially available 4-fluorophenyl-acetyl chloride (12 g, 69.5 mmol) in CH_2Cl_2 (200 mL). The reaction mixture is stirred for 2 hours at –78°C and is then slowly warmed to room temperature. The reaction mixture is filtered and the filtrate concentrated under reduced pressure to give a pale yellow oil. Purification over silica (EtOAc) affords 7.6 g (61% yield) of the desired product: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.23 (m, 2H), 6.99-6.92 (m, 2H), 3.87 (s, 2H), 3.190 (s, 2H), 3.11 (s, 3H); ESI/MS: 183.1 (M+H).

Preparation of 4-{N'-[2-(4-fluoro-phenyl)-acetyl]-N'-methyl-hydrazino}-piperidine-1-carboxylic acid *tert*-butyl ester (9). To a stirred solution of (4-fluorophenyl)-acetic acid N-methyl-hydrazide, **8**, (2 g, 11 mmol) in ethanol (20 mL) is added commercially available 4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (2.19 g, 11 mmol). The reaction mixture is refluxed for 30 minutes, then cooled to room temperature after which $NaCNBH_3$ (1.04 g, 16,5 mmol) is added. The pH of the reaction mixture is adjusted to about 3 with concentrated HCl and the reaction mixture stirred for 3 hours at room temperature. The mixture is neutralized with saturated sodium bicarbonate and extracted three times with CH_2Cl_2. The combined organic layers are dried, filtered and concentrated *in vacuo*. Purification over silica (EtOAc) affords 3.7 g (93% yield) of the desired product. ESI/MS: 366.3 (M+H).

Preparation of 4-{N'-[2-(4-fluoro-phenyl)-acetyl]-N'-methyl-N-(2-methylsulfanyl-pyrimidine-4-carbonyl)-hydrazino}-piperidine-1-carboxylic acid *tert*-butyl ester (10). To a stirred solution of 4-{N'-[2-(4-fluoro-phenyl)-acetyl]-N'-methyl-hydrazino}-piperidine-1-carboxylic acid *tert*-butyl ester, **9**, (3.7 g, 10.1 mmol) in pyridine (10 mL) is added 2-methylsulfanyl-pyrimidine-4-carbonyl chloride (2.9 g, 15.2 mmol). The reaction mixture is stirred at room temperature for 2 hours then diluted with 0.1 N HCl and extracted three times with CH_2Cl_2. The combined organic layers are dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification over silica (EtOAc/ hexanes 1:1) affords 1.058 g (20% yield) of the desired product. ESI/MS: 518.2 (M+H).

Preparation of 4-[4-(4-fluorophenyl)-2-methyl-5-(2-methylsulfanyl-pyrimidin-4-yl)-3-oxo-2,3-dihydro-pyrazol-1-yl]-piperidine-1 carboxylic acid *tert*-butyl ester (11). To a solution of 4-{N'-[2-(4-fluoro-phenyl)-acetyl]-N'-methyl-N-(2-methylsulfanyl-pyrimidine-4-carbonyl)-hydrazino}-piperidine-1-carboxylic acid *tert*-butyl ester, **10**, (1.058 g, 2.05 mmol) in DMF (2 mL) at 0°C is slowly added NaH (123 mg of a 60% dispersion in mineral oil, 3.07 mmol). The reaction mixture is stirred for 1 hour at 0°C and then quenched with 0.1 N HCl. The aqueous layer is extracted three times with CH_2Cl_2 and the combined organic layers are dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification over silica (20% MeOH/ $CHCl_3$) affords 0.743 g (73% yield) of the diesired product. ESI/MS: 500.2 (M+H).

Preparation of 4-[4-(4-fluorophenyl)-2-methyl-5-(2-methanesulfonyl-pyrimidin-4-yl)-3-oxo-2,3-dihydro-pyrazol-1-yl]-piperidine-1 carboxylic acid *tert*-butyl ester (12): To a solution of 4-[4-(4-fluorophenyl)-2-methyl-5-(2-methylsulfanyl-pyrimidin-4-yl)-3-oxo-2,3-dihydro-pyrazol-1-yl]-piperidine-1 carboxylic acid *tert*-butyl ester, **11**, (5.9 g, 12 mmol) in $CHCl_3$ (200 mL) at 0°C is added *meta*-chloroperbenzoic acid (4 g, 23.37 mmol). After stirring for 5 minutes, saturated sodium bisulfite (20 mL) is added and the reaction mixture stirred for an additional 5 minutes. The aqueous phase is extracted three times with CH_2Cl_2, the combined organic phases washed with

saturated sodium bicarbonate, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material is used without further purification.

Preparation of 4-[4-(4-fluorophenyl)-2-methyl-5-(2-phenoxy-pyrimidin-4-yl)-3-oxo-2,3-dihydro-pyrazol-1-yl]-piperidine-1 carboxylic acid *tert*-butyl ester (13): To a solution of phenol (0.11 g, 1.16 mmol) in THF (5 mL) is added NaH (0.024 g of a 60% dispersion in mineral oil, 0.58 mmol). After stirring for 5 min at room temp, a solution of 4-[4-(4-fluorophenyl)-2-methyl-5-(2-methanesulfonyl-pyrimidin-4-yl)-3-oxo-2,3-dihydro-pyrazol-1-yl]-piperidine-1 carboxylic acid *tert*-butyl ester, **12**, (0.154 g, 0.29 mmol) in THF (3 mL) is added all at once. The reaction mixture is stirred at room temp for 14 hours and then quenched by pouring into aqueous saturated $NaHCO_3$ solution. The aqueous phase is extracted three times with CH_2Cl_2, the combined organic phases washed with saturated sodium bicarbonate, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was used without further purification in the next step.

Preparation of 4-(4-fluorophenyl)-2-methyl-5-(2-phenoxy-pyrimidin-4-yl)-1-piperidin-4-yl-1,2-dihydro-pyrazol-3-one (14): To a solution of 4-[4-(4-fluorophenyl)-2-methyl-5-(2-phenoxy-pyrimidin-4-yl)-3-oxo-2,3-dihydro-pyrazol-1-yl]-piperidine-1 carboxylic acid *tert*-butyl ester, **13**, (9 g, 15.7 mmol) in CH_2Cl_2 (90 mL) was added 20% TFA in CH_2Cl_2. After stirring at room temperature for 0.5 h, the reaction mixture was concentrated *in vacuo*. Purification by preparatory HPLC afforded the desired product as the trifluoroacetate salt. ^{1}H NMR (300 MHz, $CDCl_3$)δ 8.57 (d, J = 4.8 Hz, 1H), 7.46 (dd, J = 7.8, 7.8 Hz, 2H), 7.31 (dd, J = 7.5, 7.5 Hz, 2H), 7.26-7.7.19 (m, 3H), 7.06 (dd, J = 8.7, 8.7 Hz, 2H), 6.90 (d, J = 4.8 Hz, 1H), 3.40 (m, 1H), 3.52 (s, 3H), 3.33 (m, 2H), 2.65 (m, 2H), 2.27 (m, 2H), 1.73 (m, 2H). HRMS calcd for $C_{25}H_{24}FN_5O_2$ $(M + H)^+$ 446.1992; found 446.1971.

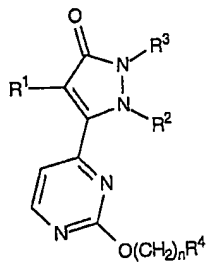
Non-limiting examples of other compounds comprising the first aspect of Category II include:

4-(4-fluorophenyl)-2-methyl-5-(2-phenoxy-pyrimidin-4-yl)-1-(*N*-methyl)piperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-(2-phenoxy-pyrimidin-4-yl)-1-benzyl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-[2-(2-fluorophenoxy)pyrimidin-4-yl]-1-piperidin-4-yl-1,2-dihydro-pyrazol-3-one;

The second aspect of Category II inflammatory cytokine release inhibiting compounds according to the present invention are 4-R^1-substituted-5-(2-R-substituted-pyrimidin-4-yl)-1,2-dihydropyrazol-3-ones having the general scaffold with the formula:



wherein the R^2 comprising a lower alkyl unit, R^3 comprising a substituted or unsubstituted ring, and the index n is 0, as defined in Table IV herein below.

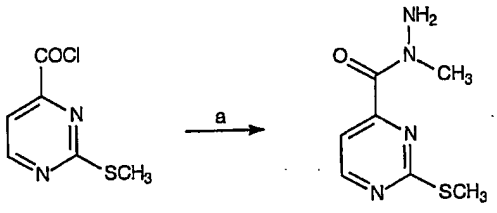
TABLE IV

No.	R^1	R^2	R^3	R^4
149	4-fluorophenyl	methyl	piperidin-4-yl	phenyl
150	4-fluorophenyl	methyl	piperidin-4-yl	2-hydroxyphenyl
151	4-fluorophenyl	methyl	piperidin-4-yl	4-hydroxyphenyl
152	4-fluorophenyl	methyl	piperidin-4-yl	2-*N*-acetylaminophenyl
153	4-fluorophenyl	methyl	piperidin-4-yl	3-*N*-acetylaminophenyl
154	4-fluorophenyl	methyl	piperidin-4-yl	2-cyanophenyl
155	4-fluorophenyl	methyl	piperidin-4-yl	4-fluorophenyl
156	4-fluorophenyl	methyl	piperidin-4-yl	benzyl
157	4-fluorophenyl	methyl	piperidin-4-yl	(S)-α-methylbenzyl
158	4-fluorophenyl	methyl	piperidin-4-yl	(R)-α-methylbenzyl
159	4-fluorophenyl	methyl	*N*-methylpiperidin-4-yl	phenyl
160	4-fluorophenyl	methyl	*N*-methylpiperidin-4-yl	2-hydroxyphenyl
161	4-fluorophenyl	methyl	*N*-methylpiperidin-4-yl	4-hydroxyphenyl
162	4-fluorophenyl	methyl	*N*-methylpiperidin-4-yl	2-*N*-acetylaminophenyl
163	4-fluorophenyl	methyl	*N*-methylpiperidin-4-yl	3-*N*-acetylaminophenyl
164	4-fluorophenyl	methyl	*N*-methylpiperidin-4-yl	2-cyanophenyl
165	4-fluorophenyl	methyl	*N*-methylpiperidin-4-yl	4-fluorophenyl
166	4-fluorophenyl	methyl	*N*-methylpiperidin-4-yl	benzyl
167	4-fluorophenyl	methyl	*N*-methylpiperidin-4-yl	(S)-α-methylbenzyl
168	4-fluorophenyl	methyl	*N*-methylpiperidin-4-yl	(R)-α-methylbenzyl
169	4-fluorophenyl	methyl	morpholin-4-yl	phenyl
170	4-fluorophenyl	methyl	morpholin-4-yl	2-hydroxyphenyl
171	4-fluorophenyl	methyl	morpholin-4-yl	4-hydroxyphenyl
172	4-fluorophenyl	methyl	morpholin-4-yl	2-*N*-acetylaminophenyl

173	4-fluorophenyl	methyl	morpholin-4-yl	3-*N*-acetylaminophenyl
174	4-fluorophenyl	methyl	morpholin-4-yl	2-cyanophenyl
175	4-fluorophenyl	methyl	morpholin-4-yl	4-fluorophenyl
176	4-fluorophenyl	methyl	morpholin-4-yl	benzyl
177	4-fluorophenyl	methyl	morpholin-4-yl	(S)-α-methylbenzyl
178	4-fluorophenyl	methyl	morpholin-4-yl	(R)-α-methylbenzyl
179	4-fluorophenyl	methyl	*N*-acetylpiperidin-4-yl	phenyl
180	4-fluorophenyl	methyl	*N*-acetylpiperidin-4-yl	2-hydroxyphenyl
181	4-fluorophenyl	methyl	*N*-acetylpiperidin-4-yl	4-hydroxyphenyl
182	4-fluorophenyl	methyl	*N*-acetylpiperidin-4-yl	2-*N*-acetylaminophenyl
183	4-fluorophenyl	methyl	*N*-acetylpiperidin-4-yl	3-*N*-acetylaminophenyl
184	4-fluorophenyl	methyl	*N*-acetylpiperidin-4-yl	2-cyanophenyl
185	4-fluorophenyl	methyl	*N*-acetylpiperidin-4-yl	4-fluorophenyl
186	4-fluorophenyl	methyl	*N*-acetylpiperidin-4-yl	benzyl
187	4-fluorophenyl	methyl	*N*-acetylpiperidin-4-yl	(S)-α-methylbenzyl
188	4-fluorophenyl	methyl	*N*-acetylpiperidin-4-yl	(R)-α-methylbenzyl

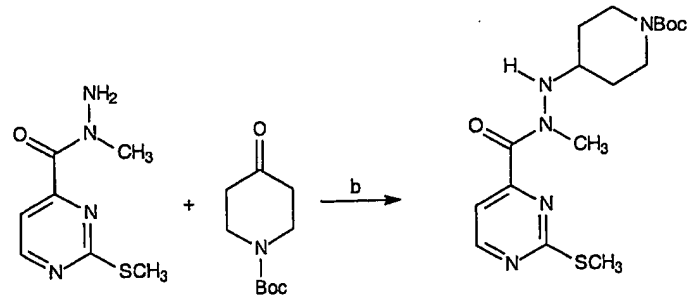
The following is an example of the preparation of compounds encompassed within the second aspect of Category II analogs according to the present invention.

Scheme IV: Preparation of Second Aspect of Category II



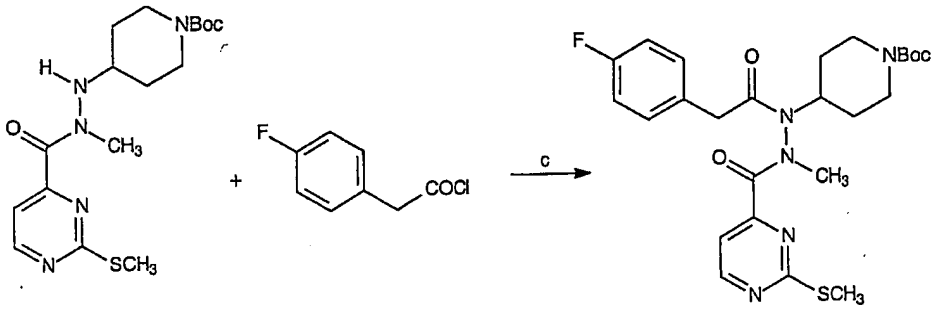
15

Reagents and conditions: (a) H_2NNHCH_3, CH_2Cl_2; -78 °C to rt, 2 hr.



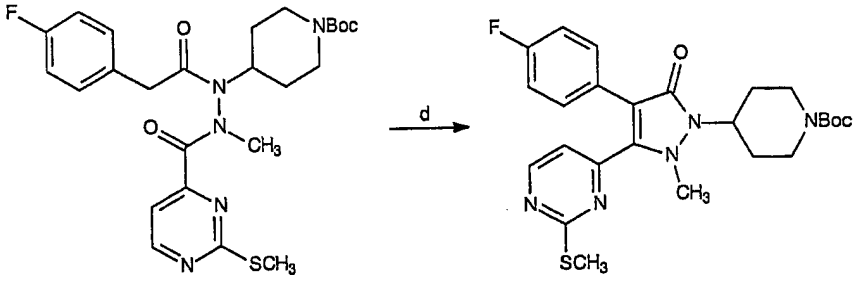
15 16

Reagents and conditions: (b) i) reflux 0.5 hr; ii) $NaCNBH_3$, HCl, EtOH; rt, 3 hr.



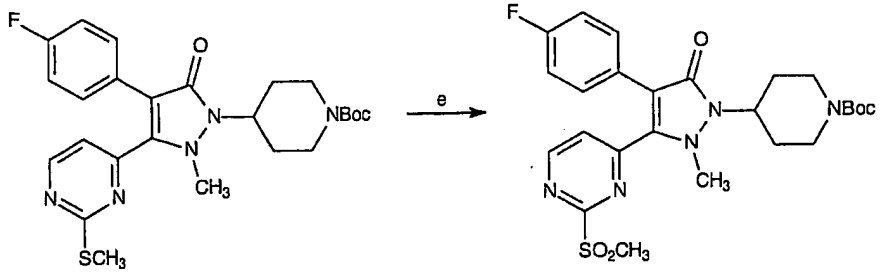
16 17

Reagents and conditions: (c) pyridine; rt, 2 hr.



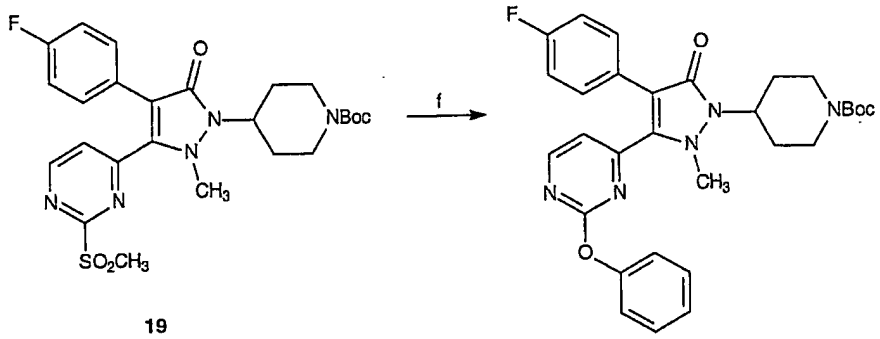
17 18

Reagents and conditions: (d) NaH, DMF; 0 °C, 1 hr.



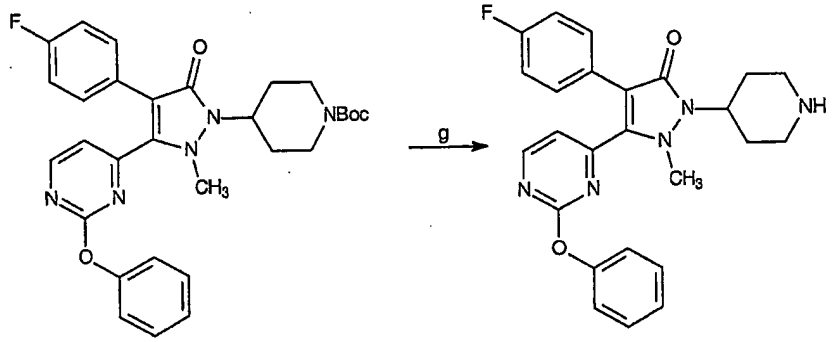
18 19

Reagents and conditions: (e) m-CPBA, $CHCl_3$; 0 °C, 5 min.



19 20

Reagents and conditions: (f) phenol, NaH, THF; rt, 14 hr.



20 21

Reagents and conditions: (g) TFA, CH_2Cl_2; rt, 30 min.

EXAMPLE 4

4-(4-Fluorophenyl)-2-piperidin-4-yl-5-(2-phenoxy-pyrimidin-4-yl)-1-methyl-1,2-dihydro-pyrazol-3-one (21)

Preparation of 2-Methylsulfanyl-pyrimidine-4-carboxylic acid N-methyl-hydrazide (15): To a –78°C stirred solution of methyl hydrazine (17 mL, 318 mmol) in CH_2Cl_2 (500 mL) is added dropwise a solution of 2-methylsulfanyl-pyrimidine-4-carbonyl chloride (20 g, 106 mmol) in CH_2Cl_2 (500 mL). The reaction mixture is stirred for 2 hours at –78°C and then slowly warmed to room temperature. The reaction mixture is concentrated under reduced pressure to give a purple oil. Purification over silica (EtOAc/ hexanes 1:1) affords 6.98 g (33% yield) of the desired compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69-8.64 (m, 1H), 7.35-7.08 (m, 1H), 3.40 (s, 3H), 3.36 (s, 2H), 2.59 (s, 3H); ESI/MS: 199.1 (M+H).

Preparation of 4-[N'-Methyl-N'-(2-methylsulfanyl-pyrimidine-4-carbonyl)-hydrazino]-piperidine-1-carboxylic acid *tert*-butyl ester (16). To a stirred solution of 2-Methylsulfanyl-pyrimidine-4-carboxylic acid N-methyl-hydrazide, **15**, (15 g, 75.8 mmol) in ethanol (60 mL) is added 4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (15.1 g, 75.8 mmol). The reaction mixture is refluxed for 1.5 hour, cooled to room temperature and $NaCNBH_3$ (7.14 g, 113.7 mmol) added. The pH of the reaction mixture is adjusted to 3 with concentrated HCl and the reaction mixture stirred for 3 hours at room temperature. The mixture is neutralized with saturated sodium bicarbonate and extracted three times with CH_2Cl_2 and the combined organic layers are dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification over silica (EtOAc) affords 19.7 g (68% yield) of the desired product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (q, J=2.9 Hz, 1H), 7.36-7.27 (m, 1H), 4.16 (q, J=6.9Hz, 1H), 3.97-3.78 (m, 2H), 3.37 (d, J=16 Hz, 3H), 2.91-2.79 (m, 2H), 2.61 (s, 3H), 1.93-1.89 (m, 2H), 1.70-1.65 (m, 2H), 1.48 (d, J=8 Hz), 9H); ESI/MS: 382.3 (M+H).

Preparation of 4-{N-[2-(4-Fluoro-phenyl)-acetyl]-N'-methyl-N'-(2-methylsulfanyl-pyrimidine-4-carbonyl)-hydrazino}-piperidine-1-carboxylic acid *tert*-butyl ester (17). To a stirred 0°C solution of 4-[N'-Methyl-N'-(2-methylsulfanyl-pyrimidine-4-carbonyl)-hydrazino]-piperidine-1-carboxylic acid tert-butyl ester, **16**, (19.8 g, 51.7 mmol) in pyridine (25 mL) is added (4-fluorophenyl)acetyl chloride (10 g, 57.9 mmol). The reaction mixture is slowly warmed to room temperature and then stirred for 2 hours. The reaction mixture is then concentrated *in vacuo*. Purification over silica (100% EtOAc) affords 42 g of the desired product: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80-8.70 (m, 1H), 7.40-7.32 (m, 1H), 7.29-7.18 (m, 2H), 7.07-6.94 (m, 2H), 4.24-4.10 (m, 3H), 3.82-3.59 (m, 2H), 3.33 (d, J=8.4 Hz, 3H), 2.88-2.67 (m, 2H), 2.60 (d, J=18.6 Hz , 3H), 1.96-1.92 (m, 2H), 1.70-1.65 (m, 2H), 1.48 (d, J=4.0 Hz, 9H); ESI/MS: 518.2 (M+H).

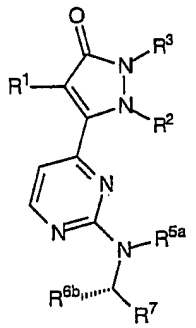
Preparation of 4-[4-(4-Fluorophenyl)-2-methyl-3-(2-methylsulfanyl-pyrimidin-4-yl)-5-oxo-2,5-dihydro-pyrazol-1-yl]-piperidine-1 carboxylic acid *tert*-butyl ester (18). To a 0°C solution of 4-{N-[2-(4-Fluoro-phenyl)-acetyl]-N'-methyl-N'-(2-methylsulfanyl-pyrimidine-4-carbonyl)-hydrazino}-piperidine-1-carboxylic acid *tert*-butyl ester, **17**, (26.7 g, 51.7 mmol) in DMF (50 mL) is

slowly added NaH (3.1 g of a 60% dispersion in mineral oil, 77.55 mmol). The reaction mixture is stirred for 0.5 h at 0°C and then quenched with 1.0 N HCl. The aqueous layer is extracted threee times with CH_2Cl_2. The combined organic layers are dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification over silica (100% EtOAc) affords 12 g (45% yield) of the desired product: ^1H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 4.9 Hz, 1H), 7.35-7.29 (m, 2H), 7. 02 (t, J=6.8 Hz, 2H), 6.85 (d, J=5.1 Hz, 1H), 4.42-4.32 (m, 3H), 3.28 (s, 3H), 2.88 (t, 12.8 Hz, 2H), 2.58 (s, 3H), 2.79-2.39 (m, 2H), 1.94 (d, J=11.7 Hz, 2H), 1.50 (s, 9H); ESI/MS: 500.3 (M+H).

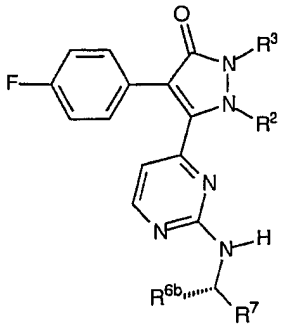
The same procedures which are used to convert compound **11** to the analog compound **14** as depicted in Scheme III, can be utilized for the conversion of compound **18** to analog compound **21** in Scheme IV.

4-(4-Fluorophenyl)-1-methyl-5-(2-phenoxy-pyrimidin-4-yl)-2-piperidin-4-yl-1,2-dihydro-pyrazol-3-one trifluoro-acetic acid salt (21): ^1H NMR (300 MHz, CD_3OD)δ 8.64 (dd, J = 5.4, 2.1 Hz, 1H), 7.44-7.05 (m, 10H), 4.61-4.47 (m, 1H), 3.55 (m, 2H), 3.39 (bs, 3H), 3.21-3.13 (m, 2H), 2.89-2.78 (m, 2H), 2.09 (m, 2H). HRMS calcd for $C_{25}H_{24}FN_5O_2$ $(M + H)^+$ 446.1992; found 446.2013.

The compounds which comprise Category III analogs of the present invention have the formula:



wherein the compounds comprising the first aspect of Category III have the formula:



wwherein R^3 is C_1-C_4 alkyl, R^7 is aryl, and R^2, R^3, R^{6b}, and R^7 are described herein below in Table V. The analogs described herein have the indicated stereochemistry when R^{6b} is not hydrogen.

TABLE V

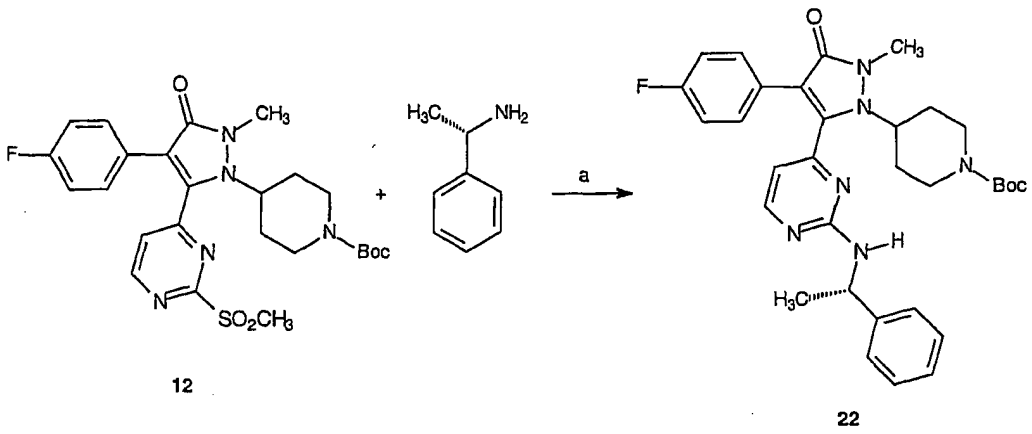
No.	R^2	R^3	R^{6b}	R^7
189	piperidin-4-yl	methyl	hydrogen	phenyl
190	piperidin-4-yl	methyl	hydrogen	4-fluorophenyl
191	piperidin-4-yl	methyl	hydrogen	2-aminophenyl
192	piperidin-4-yl	methyl	hydrogen	2-methylphenyl
193	piperidin-4-yl	methyl	hydrogen	4-methylphenyl
194	piperidin-4-yl	methyl	hydrogen	4-methoxyphenyl
195	piperidin-4-yl	methyl	hydrogen	4-(propanesulfonyl)phenyl
196	piperidin-4-yl	methyl	hydrogen	3-benzo[1,3]dioxol-5-yl
197	piperidin-4-yl	methyl	hydrogen	pyridin-2-yl
198	piperidin-4-yl	methyl	hydrogen	pyridin-3-yl
199	*N*-methylpiperidin-4-yl	methyl	hydrogen	phenyl
200	*N*-methylpiperidin-4-yl	methyl	hydrogen	4-fluorophenyl
201	*N*-methylpiperidin-4-yl	methyl	hydrogen	2-aminophenyl
202	*N*-methylpiperidin-4-yl	methyl	hydrogen	2-methylphenyl
203	*N*-methylpiperidin-4-yl	methyl	hydrogen	4-methylphenyl
204	*N*-methylpiperidin-4-yl	methyl	hydrogen	4-methoxyphenyl
205	*N*-methylpiperidin-4-yl	methyl	hydrogen	4-(propanesulfonyl)phenyl
206	*N*-methylpiperidin-4-yl	methyl	hydrogen	3-benzo[1,3]dioxol-5-yl
207	*N*-methylpiperidin-4-yl	methyl	hydrogen	pyridin-2-yl
208	*N*-methylpiperidin-4-yl	methyl	hydrogen	pyridin-3-yl
209	morpholin-4-yl	methyl	hydrogen	phenyl
210	morpholin-4-yl	methyl	hydrogen	4-fluorophenyl
211	morpholin-4-yl	methyl	hydrogen	2-aminophenyl
212	morpholin-4-yl	methyl	hydrogen	2-methylphenyl

213	morpholin-4-yl	methyl	hydrogen	4-methylphenyl
214	morpholin-4-yl	methyl	hydrogen	4-methoxyphenyl
215	morpholin-4-yl	methyl	hydrogen	4-(propanesulfonyl)phenyl
216	morpholin-4-yl	methyl	hydrogen	3-benzo[1,3]dioxol-5-yl
217	morpholin-4-yl	methyl	hydrogen	pyridin-2-yl
218	morpholin-4-yl	methyl	hydrogen	pyridin-3-yl
219	*N*-acetylpiperidin-4-yl	methyl	hydrogen	phenyl
220	*N*-acetylpiperidin-4-yl	methyl	hydrogen	4-fluorophenyl
221	*N*-acetylpiperidin-4-yl	methyl	hydrogen	2-aminophenyl
222	*N*-acetylpiperidin-4-yl	methyl	hydrogen	2-methylphenyl
223	*N*-acetylpiperidin-4-yl	methyl	hydrogen	4-methylphenyl
224	*N*-acetylpiperidin-4-yl	methyl	hydrogen	4-methoxyphenyl
225	*N*-acetylpiperidin-4-yl	methyl	hydrogen	4-(propanesulfonyl)phenyl
226	*N*-acetylpiperidin-4-yl	methyl	hydrogen	3-benzo[1,3]dioxol-5-yl
227	*N*-acetylpiperidin-4-yl	methyl	hydrogen	pyridin-2-yl
228	*N*-acetylpiperidin-4-yl	methyl	hydrogen	pyridin-3-yl
229	piperidin-4-yl	methyl	methyl	phenyl
230	piperidin-4-yl	methyl	methyl	4-fluorophenyl
231	piperidin-4-yl	methyl	methyl	2-aminophenyl
232	piperidin-4-yl	methyl	methyl	2-methylphenyl
233	piperidin-4-yl	methyl	methyl	4-methylphenyl
234	piperidin-4-yl	methyl	methyl	4-methoxyphenyl
235	piperidin-4-yl	methyl	methyl	4-(propanesulfonyl)phenyl
236	piperidin-4-yl	methyl	methyl	3-benzo[1,3]dioxol-5-yl
237	piperidin-4-yl	methyl	methyl	pyridin-2-yl
238	piperidin-4-yl	methyl	methyl	pyridin-3-yl
239	*N*-methylpiperidin-4-yl	methyl	methyl	phenyl
240	*N*-methylpiperidin-4-yl	methyl	methyl	4-fluorophenyl
241	*N*-methylpiperidin-4-yl	methyl	methyl	2-aminophenyl
242	*N*-methylpiperidin-4-yl	methyl	methyl	2-methylphenyl
243	*N*-methylpiperidin-4-yl	methyl	methyl	4-methylphenyl
244	*N*-methylpiperidin-4-yl	methyl	methyl	4-methoxyphenyl
245	*N*-methylpiperidin-4-yl	methyl	methyl	4-(propanesulfonyl)phenyl
246	*N*-methylpiperidin-4-yl	methyl	methyl	3-benzo[1,3]dioxol-5-yl
247	*N*-methylpiperidin-4-yl	methyl	methyl	pyridin-2-yl
248	*N*-methylpiperidin-4-yl	methyl	methyl	pyridin-3-yl

249	morpholin-4-yl	methyl	methyl	phenyl
250	morpholin-4-yl	methyl	methyl	4-fluorophenyl
251	morpholin-4-yl	methyl	methyl	2-aminophenyl
252	morpholin-4-yl	methyl	methyl	2-methylphenyl
253	morpholin-4-yl	methyl	methyl	4-methylphenyl
254	morpholin-4-yl	methyl	methyl	4-methoxyphenyl
255	morpholin-4-yl	methyl	methyl	4-(propanesulfonyl)phenyl
256	morpholin-4-yl	methyl	methyl	3-benzo[1,3]dioxol-5-yl
257	morpholin-4-yl	methyl	methyl	pyridin-2-yl
258	morpholin-4-yl	methyl	methyl	pyridin-3-yl
259	*N*-acetylpiperidin-4-yl	methyl	methyl	phenyl
260	*N*-acetylpiperidin-4-yl	methyl	methyl	4-fluorophenyl
261	*N*-acetylpiperidin-4-yl	methyl	methyl	2-aminophenyl
262	*N*-acetylpiperidin-4-yl	methyl	methyl	2-methylphenyl
263	*N*-acetylpiperidin-4-yl	methyl	methyl	4-methylphenyl
264	*N*-acetylpiperidin-4-yl	methyl	methyl	4-methoxyphenyl
265	*N*-acetylpiperidin-4-yl	methyl	methyl	4-(propanesulfonyl)phenyl
266	*N*-acetylpiperidin-4-yl	methyl	methyl	3-benzo[1,3]dioxol-5-yl
267	*N*-acetylpiperidin-4-yl	methyl	methyl	pyridin-2-yl
268	*N*-acetylpiperidin-4-yl	methyl	methyl	pyridin-3-yl

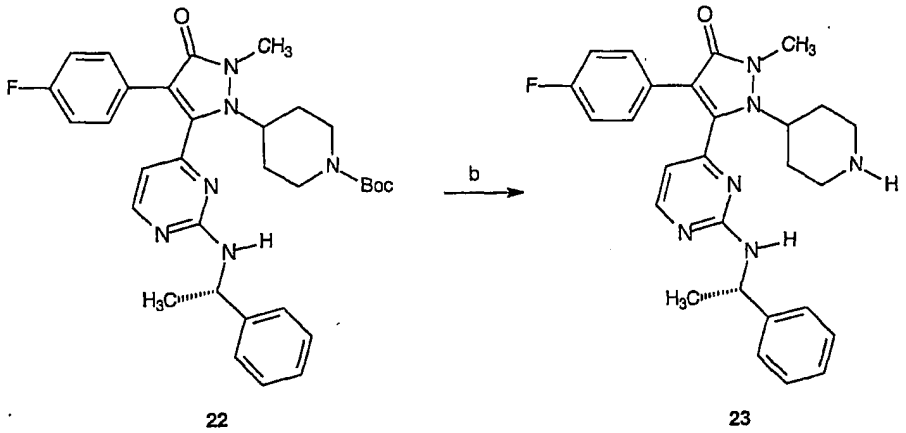
Utilizing intermediates such as compound **12**, as a convenient starting point the analogs 189-268 and others encompassed within the description of this category can be suitably prepared by the procedure outlined herein below. In the following example, R^1 is 4-fluorophenyl, however, the formulator may suitably substitute any starting material compatible with this procedure, *inter alia*, methyl phenylacetate, methyl 4-chlorophenyl-acetate, and methyl 3-(trifluoromethyl)phenyl acetate.

Scheme V: Preparation of First Aspect of Category III



12 22

Reagents and conditions: (a) toluene; 90 °C, 2 hr.



22 23

Reagents and conditions: (b) TFA, CH_2Cl_2; rt, 30 min.

EXAMPLE 5

4-(4-Fluorophenyl)-2-methyl-5-[2-(1-phenylethylamino)-pyrimidin-4-yl]-1-piperidin-4-yl-1,2-dihydropyrazol-3-one (23)

Preparation of 4-{4-(4-fluorophenyl)-2-methyl-3-oxo-5-[2-(1-phenylethylamino)-pyrimidin-4-yl]-2,3-dihydro-pyrazol-1-yl}-piperidine-1-carboxylic acid *tert*-butyl ester (22): To a solution of 4-[4-(4-fluorophenyl)-2-methyl-5-(2-methanesulfonyl-pyrimidin-4-yl)-3-oxo-2,3-dihydro-pyrazol-1-yl]-piperidine-1 carboxylic acid *tert*-butyl ester, **12**, (6 g, 12 mmol) in toluene (30 mL) is added (S)-(α)-methylbenzyl amine (1.55 mL, 24 mmol). After stirring at 90°C for 2 hours, the reaction mixture is cooled to room temperature and then concentrated *in vacuo*. Purification over silica (50% EtOAc/hexane) affords the desired product.

Preparation of 4-(4-fluorophenyl)-2-methyl-5-[2-(1-phenylethylamino)-pyrimidin-4-yl]-1-piperidin-4-yl-1,2-dihydropyrazol-3-one (23): To a solution of 4-[4-(4-fluorophenyl)-2-methyl-5-(2-methanesulfonyl-pyrimidin-4-yl)-3-oxo-2,3-dihydro-pyrazol-1-yl]-piperidine-1 carboxylic acid *tert*-butyl ester, **22**, (6 g, 12 mmol) (9 g, 15.7 mmol) in CH_2Cl_2 (90 mL) was added 20% TFA in CH_2Cl_2. After stirring at room temperature for 0.5 hour, the reaction mixture is concentrated *in vacuo*. Purification by preparatory HPLC affords the desired product as the trifluoroacetate salt. $[\alpha]_D$ -40° (c 1.8, MeOH), ^1H NMR (300 MHz, CD_3OD) δ 8.30 (d, J = 4.8 Hz, 1H), 7.42-6.96 (m, 9H) 6.50 (d, J = 4.8 Hz, 1H), 5.14-5.08 (m, 1H), 4.10-4.02 (m, 1H), 3.56 (s, 3H), 3.50-3.42 (m, 1H), 3.38-3.22 (m, 2H), 3.01-2.85 (m, 2H), 2.22-1.70 (m, 3H), 1.52 (d, J = 6.9 Hz, 3H). HRMS calcd fo $C_{27}H_{29}FN_6O$ $(M + H)^+$ 473.2465; found 473.2486.

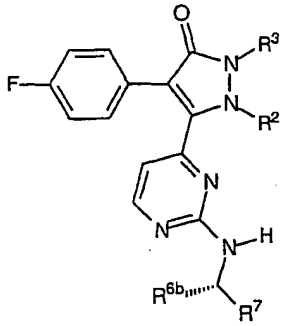
Non-limiting examples of other compounds comprising the first aspect of Category III include:

4-(4-Fluorophenyl)-2-methyl-5-{2-[1-(4-fluorophenyl)ethylamino]-pyrimidin-4-yl}-1-piperidin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-Fluorophenyl)-2-methyl-5-{2-[1-(3-fluorophenyl)ethylamino]-pyrimidin-4-yl}-1-piperidin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-Fluorophenyl)-2-methyl-5-{2-[1-(2-fluorophenyl)ethylamino]-pyrimidin-4-yl}-1-piperidin-4-yl-1,2-dihydropyrazol-3-one;

The second aspect of Category III inflammatory cytokine release inhibiting compounds according to the present invention are 4-fluorophenyl-5-(2-R-substituted-pyrimidin-4-yl)-1,2-dihydropyrazol-3-ones having the general scaffold with the formula:



wherein R^3 is C_1-C_4 alkyl, R^7 is substituted or unsubstituted C_1-C_4 alkyl, and R^2, R^3, R^{6b}, and R^7 ai described herein below in Table VI. The analogs described herein have the indicated stereochemistry when R^{6b} is not hydrogen.

TABLE VI

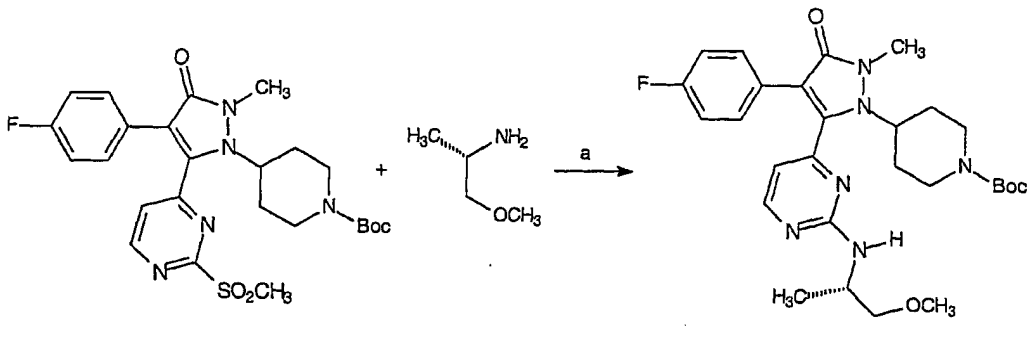
No.	R^2	R^3	R^{6b}	R^7
269	piperidin-4-yl	methyl	hydrogen	hydrogen
270	piperidin-4-yl	methyl	hydrogen	methyl
271	piperidin-4-yl	methyl	hydrogen	ethyl
272	piperidin-4-yl	methyl	hydrogen	vinyl
273	piperidin-4-yl	methyl	hydrogen	cyclopropyl
274	piperidin-4-yl	methyl	hydrogen	cyclohexyl
275	piperidin-4-yl	methyl	hydrogen	methoxymethyl
276	piperidin-4-yl	methyl	hydrogen	methoxyethyl
277	piperidin-4-yl	methyl	hydrogen	1-hydroxy-1-methylethyl
278	piperidin-4-yl	methyl	hydrogen	$-CO_2H$
279	*N*-methylpiperidin-4-yl	methyl	hydrogen	hydrogen
280	*N*-methylpiperidin-4-yl	methyl	hydrogen	methyl
281	*N*-methylpiperidin-4-yl	methyl	hydrogen	ethyl
282	*N*-methylpiperidin-4-yl	methyl	hydrogen	vinyl
283	*N*-methylpiperidin-4-yl	methyl	hydrogen	cyclopropyl
284	*N*-methylpiperidin-4-yl	methyl	hydrogen	cyclohexyl
285	*N*-methylpiperidin-4-yl	methyl	hydrogen	methoxymethyl
286	*N*-methylpiperidin-4-yl	methyl	hydrogen	methoxyethyl
287	*N*-methylpiperidin-4-yl	methyl	hydrogen	1-hydroxy-1-methylethyl
288	*N*-methylpiperidin-4-yl	methyl	hydrogen	$-CO_2H$
289	morpholin-4-yl	methyl	hydrogen	hydrogen
290	morpholin-4-yl	methyl	hydrogen	methyl
291	morpholin-4-yl	methyl	hydrogen	ethyl
292	morpholin-4-yl	methyl	hydrogen	vinyl
293	morpholin-4-yl	methyl	hydrogen	cyclopropyl
294	morpholin-4-yl	methyl	hydrogen	cyclohexyl
295	morpholin-4-yl	methyl	hydrogen	methoxymethyl
296	morpholin-4-yl	methyl	hydrogen	methoxyethyl
297	morpholin-4-yl	methyl	hydrogen	1-hydroxy-1-methylethyl
298	morpholin-4-yl	methyl	hydrogen	$-CO_2H$
299	*N*-acetylpiperidin-4-yl	methyl	hydrogen	hydrogen
300	*N*-acetylpiperidin-4-yl	methyl	hydrogen	methyl
301	*N*-acetylpiperidin-4-yl	methyl	hydrogen	ethyl
302	*N*-acetylpiperidin-4-yl	methyl	hydrogen	vinyl
303	*N*-acetylpiperidin-4-yl	methyl	hydrogen	cyclopropyl

304	*N*-acetylpiperidin-4-yl	methyl	hydrogen	cyclohexyl
305	*N*-acetylpiperidin-4-yl	methyl	hydrogen	methoxymethyl
306	*N*-acetylpiperidin-4-yl	methyl	hydrogen	methoxyethyl
307	*N*-acetylpiperidin-4-yl	methyl	hydrogen	1-hydroxy-1-methylethyl
308	*N*-acetylpiperidin-4-yl	methyl	hydrogen	$-CO_2H$
309	piperidin-4-yl	methyl	methyl	hydrogen
310	piperidin-4-yl	methyl	methyl	methyl
311	piperidin-4-yl	methyl	methyl	ethyl
312	piperidin-4-yl	methyl	methyl	vinyl
313	piperidin-4-yl	methyl	methyl	cyclopropyl
314	piperidin-4-yl	methyl	methyl	cyclohexyl
315	piperidin-4-yl	methyl	methyl	methoxymethyl
316	piperidin-4-yl	methyl	methyl	methoxyethyl
317	piperidin-4-yl	methyl	methyl	1-hydroxy-1-methylethyl
318	piperidin-4-yl	methyl	methyl	$-CO_2H$
319	*N*-methylpiperidin-4-yl	methyl	methyl	hydrogen
320	*N*-methylpiperidin-4-yl	methyl	methyl	methyl
321	*N*-methylpiperidin-4-yl	methyl	methyl	ethyl
322	*N*-methylpiperidin-4-yl	methyl	methyl	vinyl
323	*N*-methylpiperidin-4-yl	methyl	methyl	cyclopropyl
324	*N*-methylpiperidin-4-yl	methyl	methyl	cyclohexyl
325	*N*-methylpiperidin-4-yl	methyl	methyl	methoxymethyl
356	*N*-methylpiperidin-4-yl	methyl	methyl	methoxyethyl
327	*N*-methylpiperidin-4-yl	methyl	methyl	1-hydroxy-1-methylethyl
328	*N*-methylpiperidin-4-yl	methyl	methyl	$-CO_2H$
329	morpholin-4-yl	methyl	methyl	hydrogen
330	morpholin-4-yl	methyl	methyl	methyl
331	morpholin-4-yl	methyl	methyl	ethyl
332	morpholin-4-yl	methyl	methyl	vinyl
333	morpholin-4-yl	methyl	methyl	cyclopropyl
334	morpholin-4-yl	methyl	methyl	cyclohexyl
335	morpholin-4-yl	methyl	methyl	methoxymethyl
336	morpholin-4-yl	methyl	methyl	methoxyethyl
337	morpholin-4-yl	methyl	methyl	1-hydroxy-1-methylethyl
338	morpholin-4-yl	methyl	methyl	$-CO_2H$
339	*N*-acetylpiperidin-4-yl	methyl	methyl	hydrogen

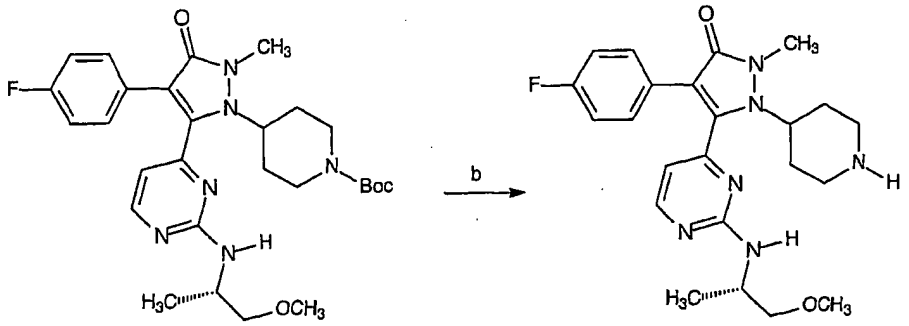
340	*N*-acetylpiperidin-4-yl	methyl	methyl	methyl
341	*N*-acetylpiperidin-4-yl	methyl	methyl	ethyl
342	*N*-acetylpiperidin-4-yl	methyl	methyl	vinyl
343	*N*-acetylpiperidin-4-yl	methyl	methyl	cyclopropyl
344	*N*-acetylpiperidin-4-yl	methyl	methyl	cyclohexyl
345	*N*-acetylpiperidin-4-yl	methyl	methyl	methoxymethyl
346	*N*-acetylpiperidin-4-yl	methyl	methyl	methoxyethyl
347	*N*-acetylpiperidin-4-yl	methyl	methyl	1-hydroxy-1-methylethyl
348	*N*-acetylpiperidin-4-yl	methyl	methyl	$-CO_2H$

Utilizing intermediates such as compound **12**, as a convenient starting point the analogs 269-348 and others encompassed within the description of this category can be suitably prepared by the procedure outlined herein below. In the following example, R^1 is 4-fluorophenyl, however, the formulator may suitably substitute any starting material compatible with this procedure, *inter alia*, methyl phenylacetate, methyl 4-chlorophenyl-acetate, and methyl 3-(trifluoromethyl)phenyl acetate.

Scheme VI: Preparation of Second Aspect of Category III



Reagents and conditions: (a) toluene; 90 °C 2 hr.



24 25

Reagents and conditions: (b) TFA, CH_2Cl_2; rt, 30 min.

EXAMPLE 6

4-(4-Fluorophenyl)-5-[2-(2-methoxy-1-(*S*)-methyl-ethylamino)pyrimidin-4-yl]-2-methyl-1-piperidin-4-yl-1,2-dihydropyrazol-3-one (25)

Preparation of 4-{4-(4-fluorophenyl)-2-methyl-3-oxo-5-[2-(2-methoxy-1-(*S*)-methyl-ethylamino)-pyrimidin-4-yl]-2,3-dihydro-pyrazol-1-yl}-piperidine-1-carboxylic acid *tert*-butyl ester (24): To a solution of 4-[4-(4-fluorophenyl)-2-methyl-5-(2-methanesulfonyl-pyrimidin-4-yl)-3-oxo-2,3-dihydro-pyrazol-1-yl]-piperidine-1 carboxylic acid *tert*-butyl ester, **12**, (6 g, 12 mmol) in toluene (30 mL) is added (*S*)-2-amino-3-methoxypropane (2.14 g, 24 mmol). After stirring at 90°C for 2 hours, the reaction mixture is cooled to room temperature and then concentrated *in vacuo*. Purification over silica (50% EtOAc/hexane) affords the desired product.

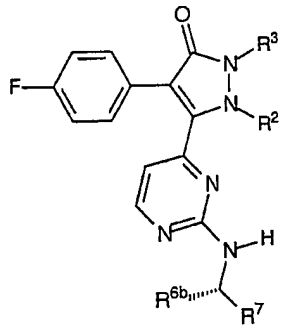
Preparation of 4-(4-fluorophenyl)-5-[2-(2-methoxy-1-(*S*)-methyl-ethylamino)-pyrimidin-4-yl]-2-methyl-1-piperidin-4-yl-1,2-dihydropyrazol-3-one (25): To a solution of 4-{4-(4-fluorophenyl)-2-methyl-3-oxo-5-[2-(2-methoxy-1-methyl-ethylamino)-pyrimidin-4-yl]-2,3-dihydro-pyrazol-1-yl}-piperidine-1-carboxylic acid *tert*-butyl ester, **24**, (6.5 g, 12 mmol) in CH_2Cl_2 (90 mL) was added 20% TFA in CH_2Cl_2. After stirring at room temperature for 0.5 hour, the reaction mixture is concentrated *in vacuo*. Purification by preparatory HPLC affords the desired product as the trifluoroacetate salt. $[\alpha]_D$ -15° (c 1.7, MeOH), ^1H NMR (300 MHz, CD_3OD) δ 8.32 (d, J = 4.8 Hz, 1H), 7.33-7.28 (m, 2H) 7.10-7.04 (m, 2H), 6.64 (d, J = 4.8 Hz, 1H), 4.35-4.19 (m, 2H), 3.63 (s, 3H), 3.59-3.35 (m, 4H), 3.37 (s, 3H), 3.12-3.01 (m, 2H), 2.26-2.17 (m, 4H), 1.21 (d, J = 6.9 Hz, 3H). HRMS calcd for $C_{23}H_{29}FN_6O_2$ $(M + H)^+$ 441.2414; found 441.2410.

Non-limiting examples of other compounds comprising the second aspect of Category III include:

4-(4-fluorophenyl)-5-[2-(2-methoxy-1-(*S*)-methyl-ethylamino)-pyrimidin-4-yl]-2-methyl-1-(*N*-acetyl)piperidin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-5-[2-(1-(*S*)-methyl-propylamino)-pyrimidin-4-yl]-2-methyl-1-(*N*-acetyl)piperidin-4-yl-1,2-dihydropyrazol-3-one;

The third aspect of Category III inflammatory cytokine release inhibiting compounds according to the present invention are 4-fluorophenyl-5-(2-R-substituted-pyrimidin-4-yl)-1,2-dihydropyrazol-3-ones having the general scaffold with the formula:



wherein R^2 is C_1-C_4 alkyl, R^7 is aryl, and R^2, R^3, R^{6b}, and R^7 are described herein below in Table VII. The analogs described herein have the indicated stereochemistry when R^{6b} is not hydrogen.

TABLE VII

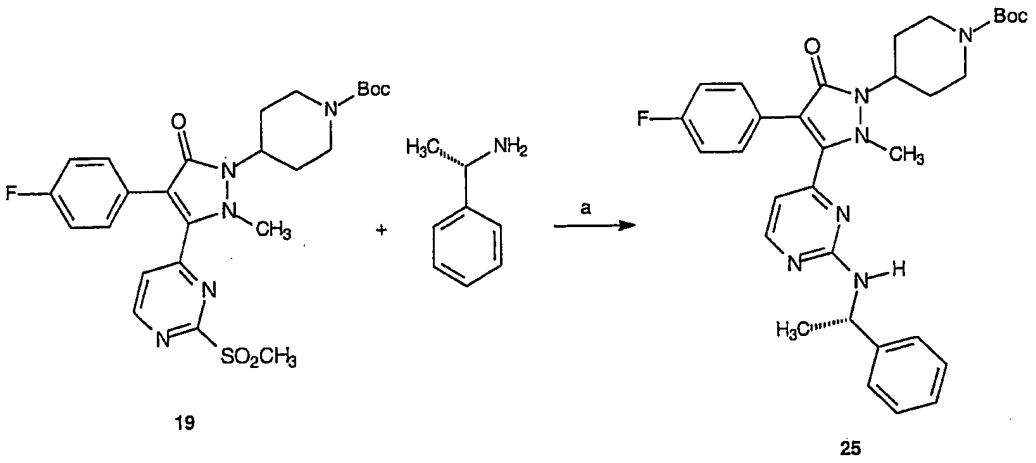
No.	R^2	R^3	R^{6b}	R^7
349	methyl	piperidin-4-yl	hydrogen	phenyl
350	methyl	piperidin-4-yl	hydrogen	4-fluorophenyl
351	methyl	piperidin-4-yl	hydrogen	2-aminophenyl
352	methyl	piperidin-4-yl	hydrogen	2-methylphenyl
353	methyl	piperidin-4-yl	hydrogen	4-methylphenyl
354	methyl	piperidin-4-yl	hydrogen	4-methoxyphenyl
355	methyl	piperidin-4-yl	hydrogen	4-(propanesulfonyl)phenyl
356	methyl	piperidin-4-yl	hydrogen	3-benzo[1,3]dioxol-5-yl
357	methyl	piperidin-4-yl	hydrogen	pyridin-2-yl
358	methyl	piperidin-4-yl	hydrogen	pyridin-3-yl
359	methyl	*N*-methylpiperidin-4-yl	hydrogen	phenyl
360	methyl	*N*-methylpiperidin-4-yl	hydrogen	4-fluorophenyl
361	methyl	*N*-methylpiperidin-4-yl	hydrogen	2-aminophenyl
362	methyl	*N*-methylpiperidin-4-yl	hydrogen	2-methylphenyl
363	methyl	*N*-methylpiperidin-4-yl	hydrogen	4-methylphenyl
364	methyl	*N*-methylpiperidin-4-yl	hydrogen	4-methoxyphenyl

365	methyl	*N*-methylpiperidin-4-yl	hydrogen	4-(propanesulfonyl)phenyl
366	methyl	*N*-methylpiperidin-4-yl	hydrogen	3-benzo[1,3]dioxol-5-yl
367	methyl	*N*-methylpiperidin-4-yl	hydrogen	pyridin-2-yl
368	methyl	*N*-methylpiperidin-4-yl	hydrogen	pyridin-3-yl
369	methyl	morpholin-4-yl	hydrogen	phenyl
370	methyl	morpholin-4-yl	hydrogen	4-fluorophenyl
371	methyl	morpholin-4-yl	hydrogen	2-aminophenyl
372	methyl	morpholin-4-yl	hydrogen	2-methylphenyl
373	methyl	morpholin-4-yl	hydrogen	4-methylphenyl
374	methyl	morpholin-4-yl	hydrogen	4-methoxyphenyl
375	methyl	morpholin-4-yl	hydrogen	4-(propanesulfonyl)phenyl
376	methyl	morpholin-4-yl	hydrogen	3-benzo[1,3]dioxol-5-yl
377	methyl	morpholin-4-yl	hydrogen	pyridin-2-yl
378	methyl	morpholin-4-yl	hydrogen	pyridin-3-yl
379	methyl	*N*-acetylpiperidin-4-yl	hydrogen	phenyl
380	methyl	*N*-acetylpiperidin-4-yl	hydrogen	4-fluorophenyl
381	methyl	*N*-acetylpiperidin-4-yl	hydrogen	2-aminophenyl
382	methyl	*N*-acetylpiperidin-4-yl	hydrogen	2-methylphenyl
383	methyl	*N*-acetylpiperidin-4-yl	hydrogen	4-methylphenyl
384	methyl	*N*-acetylpiperidin-4-yl	hydrogen	4-methoxyphenyl
385	methyl	*N*-acetylpiperidin-4-yl	hydrogen	4-(propanesulfonyl)phenyl
386	methyl	*N*-acetylpiperidin-4-yl	hydrogen	3-benzo[1,3]dioxol-5-yl
387	methyl	*N*-acetylpiperidin-4-yl	hydrogen	pyridin-2-yl
388	methyl	*N*-acetylpiperidin-4-yl	hydrogen	pyridin-3-yl
389	methyl	piperidin-4-yl	methyl	phenyl
390	methyl	piperidin-4-yl	methyl	4-fluorophenyl
391	methyl	piperidin-4-yl	methyl	2-aminophenyl
392	methyl	piperidin-4-yl	methyl	2-methylphenyl
393	methyl	piperidin-4-yl	methyl	4-methylphenyl
394	methyl	piperidin-4-yl	methyl	4-methoxyphenyl
395	methyl	piperidin-4-yl	methyl	4-(propanesulfonyl)phenyl
396	methyl	piperidin-4-yl	methyl	3-benzo[1,3]dioxol-5-yl
397	methyl	piperidin-4-yl	methyl	pyridin-2-yl
398	methyl	piperidin-4-yl	methyl	pyridin-3-yl
399	methyl	*N*-methylpiperidin-4-yl	methyl	phenyl
400	methyl	*N*-methylpiperidin-4-yl	methyl	4-fluorophenyl

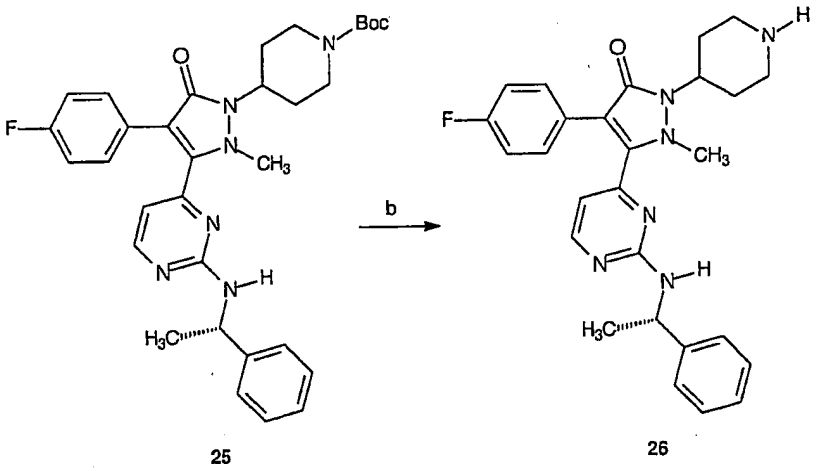
401	methyl	*N*-methylpiperidin-4-yl	methyl	2-aminophenyl
402	methyl	*N*-methylpiperidin-4-yl	methyl	2-methylphenyl
403	methyl	*N*-methylpiperidin-4-yl	methyl	4-methylphenyl
404	methyl	*N*-methylpiperidin-4-yl	methyl	4-methoxyphenyl
405	methyl	*N*-methylpiperidin-4-yl	methyl	4-(propanesulfonyl)phenyl
406	methyl	*N*-methylpiperidin-4-yl	methyl	3-benzo[1,3]dioxol-5-yl
407	methyl	*N*-methylpiperidin-4-yl	methyl	pyridin-2-yl
408	methyl	*N*-methylpiperidin-4-yl	methyl	pyridin-3-yl
409	methyl	morpholin-4-yl	methyl	phenyl
410	methyl	morpholin-4-yl	methyl	4-fluorophenyl
411	methyl	morpholin-4-yl	methyl	2-aminophenyl
412	methyl	morpholin-4-yl	methyl	2-methylphenyl
413	methyl	morpholin-4-yl	methyl	4-methylphenyl
414	methyl	morpholin-4-yl	methyl	4-methoxyphenyl
415	methyl	morpholin-4-yl	methyl	4-(propanesulfonyl)phenyl
416	methyl	morpholin-4-yl	methyl	3-benzo[1,3]dioxol-5-yl
417	methyl	morpholin-4-yl	methyl	pyridin-2-yl
418	methyl	morpholin-4-yl	methyl	pyridin-3-yl
419	methyl	*N*-acetylpiperidin-4-yl	methyl	phenyl
420	methyl	*N*-acetylpiperidin-4-yl	methyl	4-fluorophenyl
421	methyl	*N*-acetylpiperidin-4-yl	methyl	2-aminophenyl
422	methyl	*N*-acetylpiperidin-4-yl	methyl	2-methylphenyl
423	methyl	*N*-acetylpiperidin-4-yl	methyl	4-methylphenyl
424	methyl	*N*-acetylpiperidin-4-yl	methyl	4-methoxyphenyl
425	methyl	*N*-acetylpiperidin-4-yl	methyl	4-(propanesulfonyl)phenyl
426	methyl	*N*-acetylpiperidin-4-yl	methyl	3-benzo[1,3]dioxol-5-yl
427	methyl	*N*-acetylpiperidin-4-yl	methyl	pyridin-2-yl
428	methyl	*N*-acetylpiperidin-4-yl	methyl	pyridin-3-yl

Utilizing intermediates such as compound **19**, as a convenient starting point the analogs 349-428 and others encompassed within the description of this category can be suitably prepared by the procedure outlined herein below. In the following example, R^1 is 4-fluorophenyl, however, the formulator may suitably substitute any starting material compatible with this procedure, *inter alia*, methyl phenylacetate, methyl 4-chlorophenyl-acetate, and methyl 3-(trifluoromethyl)phenyl acetate.

Scheme VII: Preparation of Third Aspect of Category III



Reagents and conditions: (a) toluene; 90 °C 2 hr.



Reagents and conditions: (b) TFA, CH_2Cl_2; rt, 30 min.

EXAMPLE 7

4-(4-Fluorophenyl)-1-methyl-5-[2-(1-phenylethylamino)-pyrimidin-4-yl]-2-piperidin-4-yl-1,2-dihydropyrazol-3-one (27)

Preparation of 4-{4-(4-fluorophenyl)-2-methyl-5-oxo-3-[2-(1-phenylethylamino)-pyrimidin-4-yl]-2,5-dihydro-pyrazol-1-yl}-piperidine-1-carboxylic acid *tert*-butyl ester (26): To a solution of 4-[4-(4-fluorophenyl)-2-methyl-5-(2-methanesulfonyl-pyrimidin-4-yl)-3-oxo-2,3-dihydro-pyrazol-1-yl]-piperidine-1 carboxylic acid *tert*-butyl ester, **12**, (6 g, 12 mmol) in toluene (30 mL) is added (S)-(α)-methylbenzyl amine (1.55 mL, 24 mmol). After stirring at 90°C for 2 hours,

the reaction mixture is cooled to room temperature and then concentrated *in vacuo*. Purification over silica (50% EtOAc in hexanes) affords 5.5 g (80% yield) of the desired product: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, J = 4.9 Hz, 1H), 7.38-7.31 (m, 7H), 6.98 (t, J=8.7 Hz, 2H), 6.40 (d, J=4.9 Hz, 1H), 4.40-4.31 (m, 1H), 4.19-4.08 (m, 1H), 2.86-2.78 (m, 4H), 2.23 (t, J= 8 Hz, 2 H), 1.91 (d, J=12.4 Hz, 2H), 1.60 (d, J=6.9 Hz, 3 H), 1.52(s, 9H); ESI/MS: 573.4 (M+H).

Preparation of 4-(4-fluorophenyl)-1-methyl-5-[2-(1-phenylethylamino)-pyrimidin-4-yl]-2-piperidin-4-yl-1,2-dihydropyrazol-3-one (27): To a solution of 4-{4-(4-fluorophenyl)-2-methyl-5-oxo-3-[2-(1-phenylethylamino)-pyrimidin-4-yl]-2,5-dihydro-pyrazol-1-yl}-piperidine-1-carboxylic acid *tert*-butyl ester, **26**, (9 g, 15.7 mmol) in CH_2Cl_2 (90 mL) is added 20% TFA in CH_2Cl_2. After stirring at room temperature for 0.5 h, the reaction mixture is concentrated *in vacuo*. Purification by preparatory HPLC affords 4.2 g (45% yield) of the desired product: $[\alpha]_D$ –41.0° (c 1.7, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 8.25 (d, J = 4.8 Hz, 1H), 7.40-7.00 (m, 9H), 6.40 (d, J = 4.8 Hz, 1H), 5.11-5.05 (m, 1H), 4.51-4.41 (m, 1H), 3.61-3.55 (m, 2H), 3.33 (bd, J = 1.5 Hz, 3H), 3.24-3.05 (m, 3H), 2.92-2.75 (m, 2H), 2.19-2.10 (m, 2H), 1.52 (d, J = 6.9 Hz, 3H). HRMS calcd for $C_{27}H_{29}FN_6O$ $(M + H)^+$ 473.2465; found 473.2460.

Non-limiting examples of other compounds comprising the third aspect of Category III include:

4-(4-Fluorophenyl)-5-[2-(*S*)-(α-methylbenzylamino)pyrimidin-4-yl]-1-methyl-2-piperidin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-Fluorophenyl)-5-[2-(*S*)-(α-methylbenzylamino)pyrimidin-4-yl]-1-methyl-2-(*N*-acetyl)piperidin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-Fluorophenyl)-5-[2-(*S*)-(α-methylbenzylamino)pyrimidin-4-yl]-1-methyl-2-(*N*-methyl)piperidin-4-yl-1,2-dihydropyrazol-3-one;

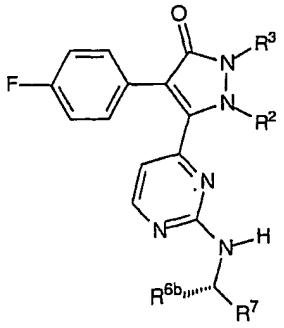
(4-{4-(4-Fluorophenyl)-2-methyl-5-oxo-3-[2-(*S*)-(α-methylbenzylamino)pyrimidin-4-yl]-2,5-dihydropyrazol-1-yl}piperidin-1-yl) acetic acid;

2-(4-{4-(4-Fluorophenyl)-2-methyl-5-oxo-3-[2-(*S*)-(α-methylbenzylamino)pyrimidin-4-yl]-2,5-dihydropyrazol-1-yl}piperidin-1-yl)-2-methyl propionic acid;

(4-{4-(4-Fluorophenyl)-2-methyl-5-oxo-3-[2-(*S*)-(α-methylbenzylamino)pyrimidin-4-yl]-2,5-dihydropyrazol-1-yl}piperidin-1-yl) acetic acid ethyl ester;

2-(4-{4-(4-Fluorophenyl)-2-methyl-5-oxo-3-[2-(*S*)-(α-methylbenzylamino)pyrimidin-4-yl]-2,5-dihydropyrazol-1-yl}piperidin-1-yl)-2-methyl propionic acid ethyl ester.

The fourth aspect of Category III inflammatory cytokine release inhibiting compounds according to the present invention are 4-fluorophenyl-5-(2-R-substituted-pyrimidin-4-yl)-1,2-dihydropyrazol-3-ones having the general scaffold with the formula:



is R^2 C_1-C_4 alkyl, R^7 is substituted or unsubstituted C_1-C_4 alkyl, and R^2, R^3, R^{6b}, and R^7 are described herein below in Table VIII. The analogs described herein have the indicated stereochemistry when R^{6b} is not hydrogen.

TABLE VIII

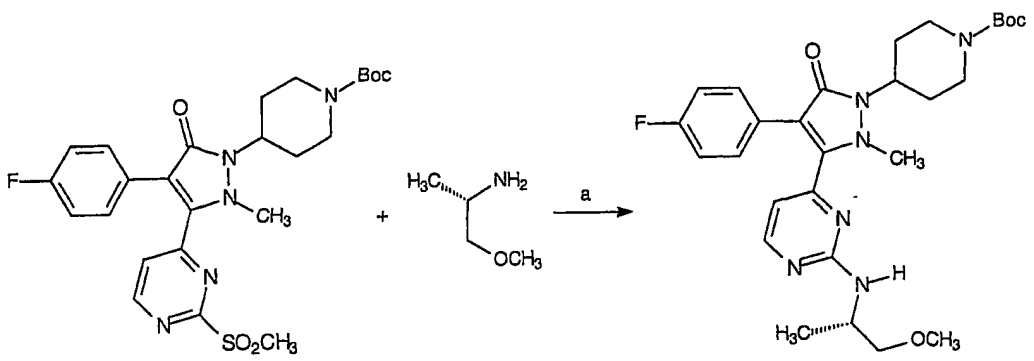
No.	R^2	R^3	R^{6b}	R^7
429	methyl	piperidin-4-yl	hydrogen	hydrogen
430	methyl	piperidin-4-yl	hydrogen	methyl
431	methyl	piperidin-4-yl	hydrogen	ethyl
432	methyl	piperidin-4-yl	hydrogen	vinyl
433	methyl	piperidin-4-yl	hydrogen	cyclopropyl
434	methyl	piperidin-4-yl	hydrogen	cyclohexyl
435	methyl	piperidin-4-yl	hydrogen	methoxymethyl
436	methyl	piperidin-4-yl	hydrogen	methoxyethyl
437	methyl	piperidin-4-yl	hydrogen	1-hydroxy-1-methylethyl
438	methyl	piperidin-4-yl	hydrogen	$-CO_2H$
439	methyl	*N*-methylpiperidin-4-yl	hydrogen	hydrogen
440	methyl	*N*-methylpiperidin-4-yl	hydrogen	methyl
441	methyl	*N*-methylpiperidin-4-yl	hydrogen	ethyl
442	methyl	*N*-methylpiperidin-4-yl	hydrogen	vinyl
443	methyl	*N*-methylpiperidin-4-yl	hydrogen	cyclopropyl
444	methyl	*N*-methylpiperidin-4-yl	hydrogen	cyclohexyl
445	methyl	*N*-methylpiperidin-4-yl	hydrogen	methoxymethyl
446	methyl	*N*-methylpiperidin-4-yl	hydrogen	methoxyethyl
447	methyl	*N*-methylpiperidin-4-yl	hydrogen	1-hydroxy-1-methylethyl
448	methyl	*N*-methylpiperidin-4-yl	hydrogen	$-CO_2H$
449	methyl	morpholin-4-yl	hydrogen	hydrogen
450	methyl	morpholin-4-yl	hydrogen	methyl

451	methyl	morpholin-4-yl	hydrogen	ethyl
452	methyl	morpholin-4-yl	hydrogen	vinyl
453	methyl	morpholin-4-yl	hydrogen	cyclopropyl
454	methyl	morpholin-4-yl	hydrogen	cyclohexyl
455	methyl	morpholin-4-yl	hydrogen	methoxymethyl
456	methyl	morpholin-4-yl	hydrogen	methoxyethyl
457	methyl	morpholin-4-yl	hydrogen	1-hydroxy-1-methylethyl
458	methyl	morpholin-4-yl	hydrogen	$-CO_2H$
459	methyl	*N*-acetylpiperidin-4-yl	hydrogen	hydrogen
460	methyl	*N*-acetylpiperidin-4-yl	hydrogen	methyl
461	methyl	*N*-acetylpiperidin-4-yl	hydrogen	ethyl
462	methyl	*N*-acetylpiperidin-4-yl	hydrogen	vinyl
463	methyl	*N*-acetylpiperidin-4-yl	hydrogen	cyclopropyl
464	methyl	*N*-acetylpiperidin-4-yl	hydrogen	cyclohexyl
465	methyl	*N*-acetylpiperidin-4-yl	hydrogen	methoxymethyl
466	methyl	*N*-acetylpiperidin-4-yl	hydrogen	methoxyethyl
467	methyl	*N*-acetylpiperidin-4-yl	hydrogen	1-hydroxy-1-methylethyl
468	methyl	*N*-acetylpiperidin-4-yl	hydrogen	$-CO_2H$
469	methyl	piperidin-4-yl	methyl	hydrogen
470	methyl	piperidin-4-yl	methyl	methyl
471	methyl	piperidin-4-yl	methyl	ethyl
472	methyl	piperidin-4-yl	methyl	vinyl
473	methyl	piperidin-4-yl	methyl	cyclopropyl
474	methyl	piperidin-4-yl	methyl	cyclohexyl
475	methyl	piperidin-4-yl	methyl	methoxymethyl
476	methyl	piperidin-4-yl	methyl	methoxyethyl
477	methyl	piperidin-4-yl	methyl	1-hydroxy-1-methylethyl
478	methyl	piperidin-4-yl	methyl	$-CO_2H$
479	methyl	*N*-methylpiperazin-4-yl	methyl	hydrogen
480	methyl	*N*-methylpiperazin-4-yl	methyl	methyl
481	methyl	*N*-methylpiperazin-4-yl	methyl	ethyl
482	methyl	*N*-methylpiperazin-4-yl	methyl	vinyl
483	methyl	*N*-methylpiperazin-4-yl	methyl	cyclopropyl
484	methyl	*N*-methylpiperazin-4-yl	methyl	cyclohexyl
485	methyl	*N*-methylpiperazin-4-yl	methyl	methoxymethyl
486	methyl	*N*-methylpiperazin-4-yl	methyl	methoxyethyl

487	methyl	*N*-methylpiperazin-4-yl	methyl	1-hydroxy-1-methylethyl
488	methyl	*N*-methylpiperazin-4-yl	methyl	$-CO_2H$
489	methyl	morpholin-4-yl	methyl	hydrogen
490	methyl	morpholin-4-yl	methyl	methyl
491	methyl	morpholin-4-yl	methyl	ethyl
492	methyl	morpholin-4-yl	methyl	vinyl
493	methyl	morpholin-4-yl	methyl	cyclopropyl
494	methyl	morpholin-4-yl	methyl	cyclohexyl
495	methyl	morpholin-4-yl	methyl	methoxymethyl
496	methyl	morpholin-4-yl	methyl	methoxyethyl
497	methyl	morpholin-4-yl	methyl	1-hydroxy-1-methylethyl
498	methyl	morpholin-4-yl	methyl	$-CO_2H$
499	methyl	*N*-acetylpiperidin-4-yl	methyl	hydrogen
500	methyl	*N*-acetylpiperidin-4-yl	methyl	methyl
501	methyl	*N*-acetylpiperidin-4-yl	methyl	ethyl
502	methyl	*N*-acetylpiperidin-4-yl	methyl	vinyl
503	methyl	*N*-acetylpiperidin-4-yl	methyl	cyclopropyl
504	methyl	*N*-acetylpiperidin-4-yl	methyl	cyclohexyl
505	methyl	*N*-acetylpiperidin-4-yl	methyl	methoxymethyl
506	methyl	*N*-acetylpiperidin-4-yl	methyl	methoxyethyl
507	methyl	*N*-acetylpiperidin-4-yl	methyl	1-hydroxy-1-methylethyl
508	methyl	*N*-acetylpiperidin-4-yl	methyl	$-CO_2H$

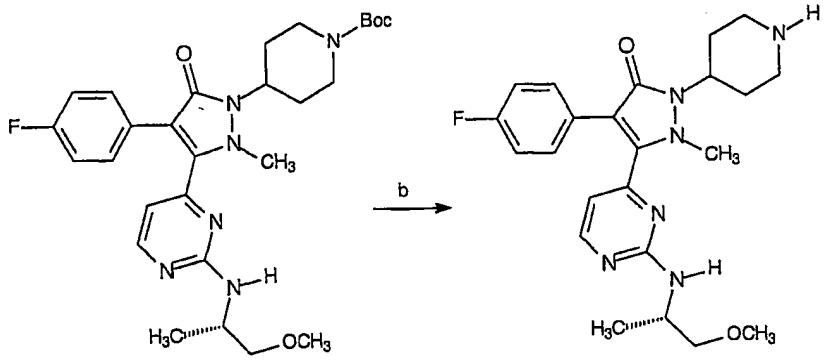
Utilizing intermediates such as compound **19**, as a convenient starting point the analogs 429-508 and others encompassed within the description of this category can be suitably prepared by the procedure outlined herein below. In the following example, R^1 is 4-fluorophenyl, however, the formulator may suitably substitute any starting material compatible with this procedure, *inter alia*, methyl phenylacetate, methyl 4-chlorophenyl-acetate, and methyl 3-(trifluoromethyl)phenyl acetate.

Scheme VIII: Preparation of Fourth Aspect of Category III



19 27

Reagents and conditions: (a) toluene; 90 °C 2 hr.



27 28

Reagents and conditions: (b) TFA, CH_2Cl_2; rt, 30 min.

EXAMPLE 8

4-(4-Fluorophenyl)-5-[2-(2-methoxy-1-(*S*)-methylethylamino)-pyrimidin-4-yl]-1-methyl-2-piperidin-4-yl-1,2-dihydropyrazol-3-one (28)

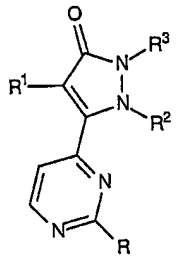
Preparation of 4-{4-(4-fluorophenyl)-3-[2-(2-methoxy-1-(*S*)-methylethylamino)-pyrimidin-4-yl]-2-methyl-5-oxo-2,5-dihydropyrazol-1-yl-1-carboxylic acid *tert*-butyl ester (27): To a solution of 4-[4-(4-fluorophenyl)-2-methyl-3-(2-methanesulfonyl-pyrimidin-4-yl)-5-oxo-2,5-dihydro-pyrazol-1-yl]-piperidine-1 carboxylic acid *tert*-butyl ester, **19**, (6 g, 12 mmol) in toluene (30 mL) is added (*S*)-2-amino-3-methoxypropane (2.14 g, 24 mmol). After stirring at 90°C for 2 hours, the reaction mixture is cooled to room temperature and then concentrated *in vacuo*. Purification over silica (50% EtOAc/hexane) affords the desired product.

Preparation of 4-(4-flu roph nyl)-5-[2-(2-methoxy-1-(*S*)-methylethylamino)-pyrimidin-4-yl]-1-methyl-2-piperidin-4-yl-1,2-dihydropyrazol-3-one (28): To a solution of 4-{4-(4-fluorophenyl)-3-[2-(2-(*S*)-methoxy-1-methylethylamino)pyrimidin-4-yl]-2-methyl-5-oxo-2,5-dihydropyrazol-1-yl-1-carboxylic acid *tert*-butyl ester, **27**, (6.5 g, 12 mmol) in CH_2Cl_2 (90 mL) was added 20% TFA in CH_2Cl_2. After stirring at room temperature for 0.5 hour, the reaction mixture is concentrated *in vacuo*. Purification by preparatory HPLC affords the desired product as the trifluoroacetate salt. ^{1}H NMR (300 MHz, CD_3OD) δ 8.30 (d, 4.8 Hz, 1H), 7.33-7.28 (m, 2H), 7.10-7.04 (m, 2H), 6.47 (d, J = 4.8Hz, 1H), 4.55-4.47 (m, 1H), 4.24-4.18 (m, 1H), 3.62-3.53 (m, 2H), 3.45-3.26 (m, 9H), 3.23-3.14 (m, 2H), 2.93-2.78 (m, 2H), 2.20-2.13 (m, 2H), 1.21 (d, J = 6.6 Hz, 3H). HRMS calcd for $C_{23}H_{29}FN_6O_2$ $(M + H)^+$ 441.2414; found 441.2425.

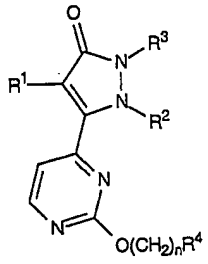
Non-limiting examples of other compounds comprising the second aspect of Category IV include:

4-(4-fluorophenyl)-5-[2-(*S*)-(1,2-dimethyl-2-hydroxypropylamino)pyrimidin-4-yl]-1-methyl-2-piperidin-4-yl-1,2-dihydropyrazol-3-one.

The compounds which comprise Category IV analogs of the present invention are 4-R^1-substituted-5-(2-R-substituted-pyrimidin-4-yl)-1,2-dihydropyrazol-3-ones having the general scaffold with the formula:



wherein the first aspect of Category IV has the formula:

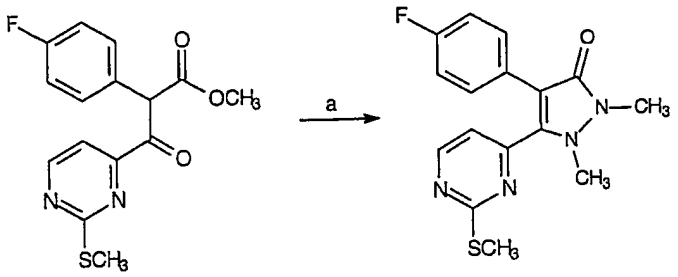


R^2 and R^3 are the same C_1-C_4 linear, branched, or cyclic alkyl and R^1, R^2, R^3 and R^4 are described herein below in Table IX. The index n can be 0 or 1.

No.	R^1	R^2/R^3	R^4
509	4-fluorophenyl	methyl	phenyl
510	4-fluorophenyl	methyl	2-fluorophenyl
511	4-fluorophenyl	methyl	3-fluorophenyl
512	4-fluorophenyl	methyl	4-fluorophenyl
513	4-fluorophenyl	methyl	2,6-difluorophenyl
514	4-fluorophenyl	methyl	2-cyanophenyl
515	4-fluorophenyl	methyl	3-cyanophenyl
516	4-fluorophenyl	methyl	2-trifluoromethylphenyl
517	4-fluorophenyl	methyl	4-trifluoromethylphenyl
518	4-fluorophenyl	methyl	*N*-methylpiperadin-4-yl
519	4-fluorophenyl	methyl	4-methylphenyl
520	4-fluorophenyl	methyl	2,4-dimethylphenyl
521	4-fluorophenyl	methyl	3-*N*-acetylaminophenyl
522	4-fluorophenyl	methyl	pyran-4-yl
523	4-fluorophenyl	methyl	4-methoxyphenyl
524	4-fluorophenyl	methyl	3-benzo[1,3]dioxol-5-yl
525	4-fluorophenyl	ethyl	phenyl
526	4-fluorophenyl	ethyl	2-fluorophenyl
527	4-fluorophenyl	ethyl	3-fluorophenyl
528	4-fluorophenyl	ethyl	4-fluorophenyl
529	4-fluorophenyl	ethyl	2,6-difluorophenyl
530	4-fluorophenyl	ethyl	2-cyanophenyl
531	4-fluorophenyl	ethyl	3-cyanophenyl
532	4-fluorophenyl	ethyl	2-trifluoromethylphenyl
533	4-fluorophenyl	ethyl	4-trifluoromethylphenyl
534	4-fluorophenyl	ethyl	*N*-methylpiperadin-4-yl
535	4-fluorophenyl	ethyl	4-methylphenyl
536	4-fluorophenyl	ethyl	2,4-dimethylphenyl
537	4-fluorophenyl	ethyl	3-*N*-acetylaminophenyl
538	4-fluorophenyl	ethyl	pyran-4-yl
539	4-fluorophenyl	ethyl	4-methoxyphenyl
540	4-fluorophenyl	ethyl	3-benzo[1,3]dioxol-5-yl

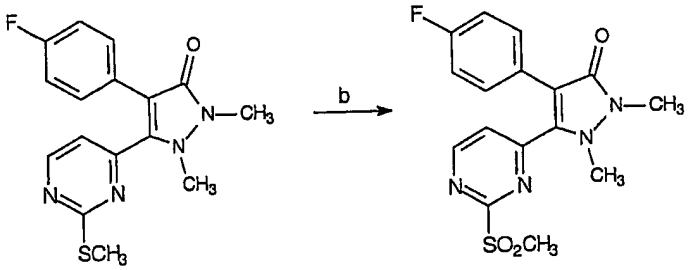
Utilizing intermediates such as compound **3**, as a convenient starting point the analogs 509-540 and others encompassed within the description of this category can be suitably prepared by the procedure outlined herein below. In the following example the formulator may suitably substitute any starting material compatible with this procedure, *inter alia*, methyl phenylacetate, methyl 4-chlorophenyl-acetate, and methyl 3-(trifluoromethyl)phenyl acetate. In addition, other alkyl hydrazines, for example, 1,2-diethylhydrazine dihydrochloride, can be substituted for 1,2-dimethylhydrazine dihydrochloride.

Scheme IX: Preparation of First Aspect of Category IV



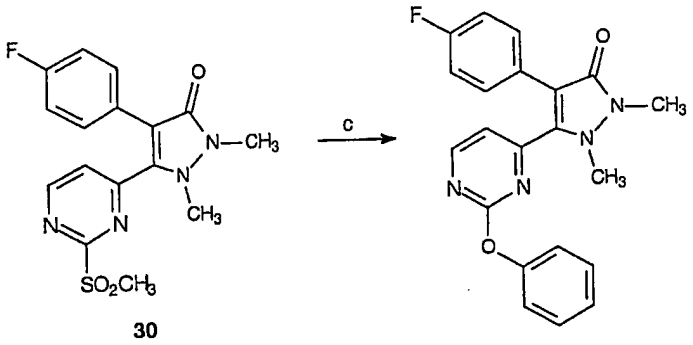
3 **29**

Reagents and conditions: (a) $CH_3NHNHCH_3$, ethanol; reflux, 5 hr.



29 **30**

Reagents and conditions: (b) Oxone®, MeOH/THF/H_2O; rt, 5 hr.



30 31

Reagents and conditions: (c) phenol, NaH, THF; rt, 14 hr.

EXAMPLE 9

4-(4-Fluorophenyl)-1,2-dimethyl-5-(2-phenoxypyrimidin-4-yl)-1,2-dihydropyrazol-3-one (31)

Preparation of 4-(4-fluorophenyl)-1,2-dimethyl-5-(2-methylsulfanyl-pyrimidin-4-yl)-1,2-dihydropyrazol-3-one (29): To a solution of **4** (4.0 g, 12.5 mmol) in ethanol (60 mL) was added 1,2-dimethylhydrazine dihydrochloride (2.5g, 18.8 mmol). After refluxing the mixture at 78 °C for 5 days, the solution was cooled to room temp. and partitioned between EtOAc (100 mL) and aqueous saturated $NaHCO_3$ solution (100 mL). The organic phase was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (biotage system) (5% EtOAc/hexanes) to yield 1.4 g (33%) of **5** as a yellow solid: ^{1}H NMR (300MHz, $CDCl_3$) δ 8.49 (d, J = 5.1 Hz, 2H), 7.31-7.36 (m, 2H), 6.83-7.05 (m, 2H), 6.83 (d, J = 5.1 Hz, 1H), 3.55 (s, 3H), 3.40 (s, 3H), 2.60 (s, 3H); MS-ESI m/z 330 $(M+H)^+$.

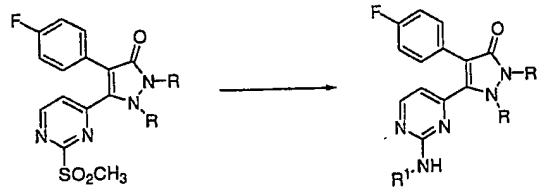
Preparation of 4-(4-fluorophenyl)-1,2-dimethyl-5-(2-methanesulfonyl-pyrimidin-4-yl)-1,2-dihydropyrazol-3-one (30): To a solution 2-(4-fluorophenyl)-3-(2-methylsulfanyl-pyrimidin-4-yl)-3-oxo-propionic acid methyl ester, **3**, (1.4 g, 4.1 mmol) in THF (25 mL) and MeOH (25 mL) is added dropwise a solution of Oxone® (10.1g, 16.4 mmol) in water (40 mL). After stirring at room temperature for 5 hours, the reaction mixture is concentrated *in vacuo*. The resulting residue is diluted with CH_2Cl_2 (150 mL) and washed with aqueous saturated $NaHCO_3$ solution (2 x 50 mL). The aqueous phase is extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic phases dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 1.1 g (72% yield) of the desired product as a yellow solid which is used without further purification: MS-ESI m/z 363 $[M+H]^+$.

Preparation of 4-(4-fluorophenyl)-1,2-dimethyl-5-(2-phenoxypyrimidin-4-yl)-1,2-dihydropyrazol-3-on (31): To a solution of phenol (0.12 g, 1.29 mmol) in THF (5 mL) is added sodium hydride (0.04 g, 1.08 mmol). After stirring at room temperature for 10 min, a solution of 4-

(4-fluorophenyl)-1,2-dimethyl-5-(2-methanesulfonyl-pyrimidin-4-yl)-1,2-dihydropyrazol-3-one, **30**, (0.20 g, 0.55 mmol) in THF (5 mL) is added to the reaction mixture. The mixture is stirred at room temperature for 4 hours. The reaction is then quenched with H_2O and diluted with EtOAc. The organic phase is washed with 1N NaOH (x2), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue is purified by preparatory HPLC to the desired product: ^1H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, J = 4.8 Hz, 1H), 7.48 (t, J = 8.1 Hz, 2H), 7.36-7.31 (m, 3H), 7.24 (dd, J = 7.5 , 1.2 Hz, 2H), 7.04 (t, J = 9.0 Hz, 2H), 6.94 (d, J = 5.1 Hz, 1H), 3.53 (s, 3H), 3.38 (s, 3H); HRMS calcd for $C_{21}H_{18}FN_4O_2$ $(M + H)^+$ 377.1418; found 377.1397.

1,2-Diethyl-4-(4-fluorophenyl)-5-(2-phenoxypyrimidin-4-yl)-1,2-dihydropyrazol-3-one; ^1H NMR (300MHz, $CDCl_3$) δ 8.50 (d, *J* = 4.9 Hz, 1H), 7.51 – 7.24 (m, 7H), 7.03 (t, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 1H), 4.01 (q, *J* = 7.1 Hz, 2H), 3.90 (q, *J* = 6.9 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H), 0.883 (t, *J* = 6.9 Hz, 3H); MS-ESI *m/z* 405 $[M+H]^+$; HRMS *m/z* calcd for $C_{23}H_{22}FN_4O_2$ $[M+H^+]$ 405.1727, found 405.1715.

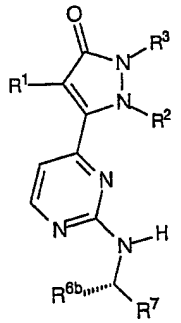
The second aspect of Category IV inflammatory cytokine release inhibiting compounds



7 (R = Me)
8 (R = Et)

9

according to the present invention are 4-fluorophenyl-5-(2-R-substituted-pyrimidin-4-yl)-1,2-dihydropyrazol-3-ones having the general scaffold with the formula:



R^2 and R^3 are the same C_1-C_4 linear, branched, or cyclic alkyl and R^2, R^3, R^{6b}, and R^7 are described herein below in Table X. The analogs described herein have the indicated stereochemistry when R^{6b} is not hydrogen.

TABLE X

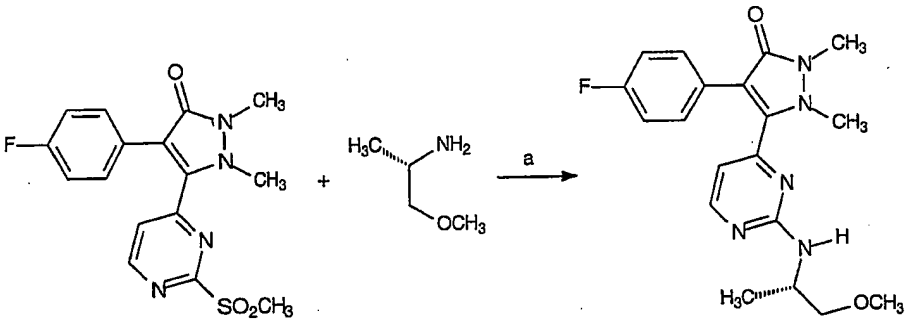
No.	R^1	R^2/R^3	R^{66}	R^7
541	4-fluorophenyl	methyl	hydrogen	phenyl
542	4-fluorophenyl	methyl	hydrogen	4-fluorophenyl
543	4-fluorophenyl	methyl	hydrogen	2-aminophenyl
544	4-fluorophenyl	methyl	hydrogen	2-methylphenyl
545	4-fluorophenyl	methyl	hydrogen	4-methylphenyl
546	4-fluorophenyl	methyl	hydrogen	4-methoxyphenyl
547	4-fluorophenyl	methyl	hydrogen	4-(propanesulfonyl)phenyl
548	4-fluorophenyl	methyl	hydrogen	3-benzo[1,3]dioxol-5-yl
549	4-fluorophenyl	methyl	hydrogen	pyridin-2-yl
550	4-fluorophenyl	methyl	hydrogen	pyridin-3-yl
551	4-fluorophenyl	methyl	methyl	phenyl
552	4-fluorophenyl	methyl	methyl	4-fluorophenyl
553	4-fluorophenyl	methyl	methyl	2-aminophenyl
554	4-fluorophenyl	methyl	methyl	2-methylphenyl
555	4-fluorophenyl	methyl	methyl	4-methylphenyl
556	4-fluorophenyl	methyl	methyl	4-methoxyphenyl
557	4-fluorophenyl	methyl	methyl	4-(propanesulfonyl)phenyl
558	4-fluorophenyl	methyl	methyl	3-benzo[1,3]dioxol-5-yl
559	4-fluorophenyl	methyl	methyl	pyridin-2-yl
560	4-fluorophenyl	methyl	methyl	pyridin-3-yl
561	4-fluorophenyl	methyl	hydrogen	H
562	4-fluorophenyl	methyl	hydrogen	methyl
563	4-fluorophenyl	methyl	hydrogen	ethyl
564	4-fluorophenyl	methyl	hydrogen	vinyl
565	4-fluorophenyl	methyl	hydrogen	cyclopropyl
566	4-fluorophenyl	methyl	hydrogen	cyclohexyl
567	4-fluorophenyl	methyl	hydrogen	methoxymethyl
568	4-fluorophenyl	methyl	hydrogen	methoxyethyl
569	4-fluorophenyl	methyl	hydrogen	1-hydroxy-1-methylethyl
570	4-fluorophenyl	methyl	hydrogen	$-CO_2H$
571	4-fluorophenyl	methyl	methyl	H
572	4-fluorophenyl	methyl	methyl	methyl
573	4-fluorophenyl	methyl	methyl	ethyl
574	4-fluorophenyl	methyl	methyl	vinyl

575	4-fluorophenyl	methyl	methyl	cyclopropyl
576	4-fluorophenyl	methyl	methyl	cyclohexyl
577	4-fluorophenyl	methyl	methyl	methoxymethyl
578	4-fluorophenyl	methyl	methyl	methoxyethyl
579	4-fluorophenyl	methyl	methyl	1-hydroxy-1-methylethyl
580	4-fluorophenyl	methyl	methyl	$-CO_2H$
581	4-fluorophenyl	ethyl	hydrogen	phenyl
582	4-fluorophenyl	ethyl	hydrogen	4-fluorophenyl
583	4-fluorophenyl	ethyl	hydrogen	2-aminophenyl
584	4-fluorophenyl	ethyl	hydrogen	2-methylphenyl
585	4-fluorophenyl	ethyl	hydrogen	4-methylphenyl
586	4-fluorophenyl	ethyl	hydrogen	4-methoxyphenyl
587	4-fluorophenyl	ethyl	hydrogen	4-(propanesulfonyl)phenyl
588	4-fluorophenyl	ethyl	hydrogen	3-benzo[1,3]dioxol-5-yl
589	4-fluorophenyl	ethyl	hydrogen	pyridin-2-yl
590	4-fluorophenyl	ethyl	hydrogen	pyridin-3-yl
591	4-fluorophenyl	ethyl	methyl	phenyl
592	4-fluorophenyl	ethyl	methyl	4-fluorophenyl
593	4-fluorophenyl	ethyl	methyl	2-aminophenyl
594	4-fluorophenyl	ethyl	methyl	2-methylphenyl
595	4-fluorophenyl	ethyl	methyl	4-methylphenyl
596	4-fluorophenyl	ethyl	methyl	4-methoxyphenyl
597	4-fluorophenyl	ethyl	methyl	4-(propanesulfonyl)phenyl
598	4-fluorophenyl	ethyl	methyl	3-benzo[1,3]dioxol-5-yl
599	4-fluorophenyl	ethyl	methyl	pyridin-2-yl
600	4-fluorophenyl	ethyl	methyl	pyridin-3-yl
601	4-fluorophenyl	ethyl	hydrogen	H
602	4-fluorophenyl	ethyl	hydrogen	methyl
603	4-fluorophenyl	ethyl	hydrogen	ethyl
604	4-fluorophenyl	ethyl	hydrogen	vinyl
605	4-fluorophenyl	ethyl	hydrogen	cyclopropyl
606	4-fluorophenyl	ethyl	hydrogen	cyclohexyl
607	4-fluorophenyl	ethyl	hydrogen	methoxymethyl
608	4-fluorophenyl	ethyl	hydrogen	methoxyethyl
609	4-fluorophenyl	ethyl	hydrogen	1-hydroxy-1-methylethyl
610	4-fluorophenyl	ethyl	hydrogen	$-CO_2H$

611	4-fluorophenyl	ethyl	methyl	H
612	4-fluorophenyl	ethyl	methyl	methyl
613	4-fluorophenyl	ethyl	methyl	ethyl
614	4-fluorophenyl	ethyl	methyl	vinyl
615	4-fluorophenyl	ethyl	methyl	cyclopropyl
616	4-fluorophenyl	ethyl	methyl	cyclohexyl
617	4-fluorophenyl	ethyl	methyl	methoxymethyl
618	4-fluorophenyl	ethyl	methyl	methoxyethyl
619	4-fluorophenyl	ethyl	methyl	1-hydroxy-1-methylethyl
620	4-fluorophenyl	ethyl	methyl	$-CO_2H$

Utilizing intermediates such as compound **30**, as a convenient starting point the analogs 540-620 and others encompassed within the description of this category can be suitably prepared by the procedure outlined herein below. In the following example the formulator may suitably substitute any starting material compatible with this procedure, *inter alia*, methyl phenylacetate, methyl 4-chlorophenyl-acetate, and methyl 3-(trifluoromethyl)phenyl acetate. In addition, other alkyl hydrazines, for example, 1,2-diethylhydrazine dihydrochloride, can be substituted for 1,2-dimethylhydrazine dihydrochloride.

Scheme X: Preparation of Second Aspect of Category IV



30 32

Reagents and conditions: (a) toluene; 140 °C, 2 hr.

EXAMPLE 10

4-(4-Fluorophenyl)-1,2-dimethyl-5-(2-methoxy-1-(*S*)-methylethylamino)-pyrimidin-4-yl]-)-1,2-dihydropyrazol-3-on (32)

Preparation of 4-(4-Fluorophenyl)-1,2-dimethyl-5-(2-methoxy-1-(*S*)-methylethyl-amino)-pyrimidin-4-yl]-)-1,2-dihydropyrazol-3-one (32): To a solution of 4-(4-fluorophenyl)-1,2-dimethyl-5-(2-methanesulfonyl-pyrimidin-4-yl)-1,2-dihydropyrazol-3-one, **30**, (0.20 g, 0.55 mmol) in toluene (5 mL) is added (*S*)-2-amino-3-methoxypropane (2.14 g, 24 mmol). The reaction is refluxed at 140 °C for 2 hours then concentrated *in vacuo.* The crude residue is purified by preparative HPLC to afford 66 mg (43% yield) of the desired product as a yellow solid: $[\alpha]^{25}_D$ = –22° (*c* 0.14, MeOH); ^{1}H NMR (300MHz, $CDCl_3$) δ 8.25 (d, *J* = 5.1 Hz, 1H), 7.41-7.35 (m, 2H), 7.03- 6.96 (m, 2H), 6.41 (d, *J* = 4.8 Hz,1H), 5.57 (d, *J* = 7.8 Hz, 1H), 4.29-4.24 (m, 1H), 3.52 (s, 3H) 3.46 (m, 2H), 3.40 (s, 3H) 3.35 (s, 3H), 1.29 (d, *J* = 6.6, 3H); MS-ESI *m/z* 372 $[M+H]^+$. HRMS *m/z* calcd for $C_{19}H_{23}FN_5O_2$ $[M+H^+]$ 372.1836, found 372.1824.

1,2-Dimethyl-4-(4-fluorophenyl)-5-[2-(*S*)-(α-methylbenzylamino)pyrimidin-4-yl]-1,2-dihydropyrazol-3-one; $[\alpha]^{25}_D$ = –3° (*c* 0.17, MeOH); ^{1}H NMR (300MHz, $CDCl_3$) δ 8.28 (d, *J* = 4.9 Hz, 1H), 7.35–7.30 (m, 2H), 7.05 (t, *J* = 8.8 Hz, 2H), 6.46 (d, *J* = 4.8 Hz, 1H), 4.02 (m, 1H), 3.61 (s, 3H), 3.57 (s, 3H), 1.24 (s, 3H), 1.23 (s, 3H), 1.21 (d, *J* = 6.9 Hz, 3H); MS-ESI *m/z* 386 $[M+H^+]$; HRMS *m/z* calcd for $C_{20}H_{25}FN_5O_2$ $[M+H^+]$ 386.1992, found 386.1977.

1,2-Dimethyl-4-(4-fluorophenyl)-5-{2-(*S*)-[1-(4-fluorophenyl)ethylamino]pyrimidin-4-yl}-1,2-dihydropyrazol-3-one; $[\alpha]^{25}_D$ = –78° (*c* 0.18, MeOH); ^{1}H NMR (300MHz, $CDCl_3$) δ 8.23 (d, *J* = 4.8 Hz, 1H), 7.40–7.29 (m, 4H), 7.08–6.96 (m, 4H), 5.81 (br s, 1H), 5.18–5.13 (m, 1H), 3.49 (s, 3H), 3.06 (br s, 3H), 1.59 (d, *J* = 6.9 Hz, 3H); MS-ESI *m/z* 422 $[M+H^+]$; HRMS *m/z* calcd for $C_{23}H_{22}F_2N_5O$ $[M+H^+]$ 422.1792, found 422.1788.

1,2-Dimethyl-4-(4-fluorophenyl)-5-[2-(*S*)-(1-methylpropylamino)pyrimidin-4-yl]-1,2-dihydro-pyrazol-3-one; $[\alpha]^{25}_D$ = +14° (*c* 0.185, MeOH); ^{1}H NMR (300MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.35 (m, 2H), 7.01 (t, *J* = 8.7, 2H), 6.41 (d, *J* = 4.8 Hz, 1H), 4.03 (m, 1H), 3.53 (s, 3H), 3.36 (s, 3H) 1.25 (d, *J* = 6.3 Hz, 3H), 1.0 (t, *J* = 7.5, 3H); MS-APCI *m/z* 356 $[M+H]^+$. HRMS *m/z* calcd for $C_{19}H_{23}FN_5O$ $[M+H^+]$ 356.1887, found 356.1883.

1,2-Dimethyl-4-(4-fluorophenyl)-5-[2-(*S*)-(1,2-dimethyl-2-hydroxypropylamino)-pyrimidin-4-yl]-1,2-dihydro-pyrazol-3-one; ^{1}H NMR (300MHz, $CDCl_3$) δ 8.28 (d, *J* = 5.1 Hz, 1H), 7.36 (dd, *J* = 5.5, 8.8 Hz, 2H), 6.97 (t, *J* = 8.8 Hz, 2H), 6.49 (d, *J* = 4.8 Hz, 1H), 3.95 (br s, 1H), 3.80 (m, 2H), 3.53 (s, 3H), 3.33 (s, 3H), 3.04–2.89 (m, 2H), 3.95–2.89 (m, 2H), 2.31–2.02 (m, 2H), 1.95–1.83 (m, 2H), 1.10 (t, *J* = 7.5 Hz, 3H); MS-ESI *m/z* 489 $[M+H]^+$; HRMS *m/z* calcd for $C_{23}H_{30}FN_6O_3S$ $[M+H^+]$ 488.2084, found 489.2086.

1,2-Dimethyl-4-(4-fluorophenyl)-5-[2-(*S*)-(1-methyl-2-methoxyethylamino)pyrimidin-4-yl]-1,2-dihydropyrazol-3-one; $[\alpha]^{25}_D = -22°$ (*c* 0.14, MeOH); ^{1}H NMR (300MHz, $CDCl_3$) δ 8.25 (d, *J* = 5.1 Hz, 1H), 7.41-7.35 (m, 2H), 7.03- 6.96 (m, 2H), 6.41 (d, *J* = 4.8 Hz,1H), 5.57 (d, *J* = 7.8 Hz, 1H), 4.29-4.24 (m, 1H), 3.52 (s, 3H) 3.46 (m, 2H), 3.40 (s, 3H) 3.35 (s, 3H), 1.29 (d, *J* = 6.6, 3H); MS-ESI *m/z* 372 $[M+H]^+$. HRMS *m/z* calcd for $C_{19}H_{23}FN_5O_2$ $[M+H^+]$ 372.1836, found 372.1824.

1,2-Dimethyl-4-(4-fluorophenyl)-5-[2-(isopropylamino)pyrimidin-4-yl]-1,2-dihydro-pyrazol-3-one; $[\alpha]^{25}_D = -22°$ (*c* 0.14, MeOH); ^{1}H NMR (300MHz, $CDCl_3$) δ 8.25 (d, *J* = 5.1 Hz, 1H), 7.41-7.35 (m, 2H), 7.03- 6.96 (m, 2H), 6.41 (d, *J* = 4.8 Hz,1H), 5.57 (d, *J* = 7.8 Hz, 1H), 4.29-4.24 (m, 1H), 3.52 (s, 3H) 3.46 (m, 2H), 3.40 (s, 3H) 3.35 (s, 3H), 1.29 (d, *J* = 6.6, 3H); MS-ESI *m/z* 372 $[M+H]^+$. HRMS *m/z* calcd for $C_{19}H_{23}FN_5O_2$ $[M+H^+]$ 372.1836, found 372.1824.

1,2-Dimethyl-4-(4-fluorophenyl)-5-[2-(pyridin-4-ylamino)pyrimidin-4-yl]-1,2-dihydro-pyrazol-3-one; ^{1}H NMR (300MHz, CD_3OD) δ 8.47 (d, *J* = 6.0 Hz, 2H), 8.32 (d, *J* = 4.9 Hz, 1H), 7.41 (d, *J* = 5.3 Hz, 1H), 7.27 (m, 2H), 7.03 (t, *J* = 8.8 Hz, 2H), 6.51 (d, *J* = 4.9 Hz, 1H), 3.57 (s, 3H), 3.34 (s, 3H); MS-ESI *m/z* 391$[M+H^+]$; HRMS *m/z* calcd for $C_{21}H_{20}FN_6O$ $[M+H^+]$ 391.1683, found 391.1668.

1,2-Dimethyl-4-(4-fluorophenyl)-5-[2-(pyridin-3-ylamino)pyrimidin-4-yl]-1,2-dihydro-pyrazol-3-one; ^{1}H NMR (300MHz, $CDCl_3$) δ 8.62 (d, *J* = 5.9 Hz, 1H), 8.32 (d, *J* = 4.9 Hz, 1H), 7.71 (m, 1H), 7.38 (m, 2H), 7.26 (m, 1H), 6.99 (t, *J* = 8.8 Hz, 2H), 6.52 (m, 1H), 6.46 (d, *J* = 4.9 Hz, 1H), 4.79 (d, *J* = 5.1 Hz, 2H), 3.52 (s, 3H), 3.30 (s, 3H); MS-ESI *m/z* 391$[M+H]^+$; HRMS *m/z* calcd for $C_{21}H_{20}FN_6O$ $[M+H^+]$ 391.1683, found 391.1684.

1,2-Dimethyl-4-(4-fluorophenyl)-5-[2-(pyridin-2-ylamino)pyrimidin-4-yl]-1,2-dihydro-pyrazol-3-one; ^{1}H NMR (300MHz, $CDCl_3$) δ 8.62 (d, *J* = 4.0 Hz, 1H), 8.32 (d, *J* = 5.1 Hz, 1H), 7.71 (dt, *J* = 1.5, 7.7 Hz, 1H), 7.61–7.60 (m, 1H), 7.41–7.32 (m, 2H), 7.29–7.23 (m, 1H), 7.00 (t, *J* = 8.8 Hz, 2H), 6.55 (br s, 1H), 6.47 (d, *J* = 4.9 Hz, 1H), 4.80 (d, *J* = 5.1 Hz, 2H), 3.53 (s, 3H), 3.31 (br s, 3H); MS-ESI *m/z* 391$[M+H^+]$; HRMS *m/z* calcd for $C_{21}H_{20}FN_6O$ $[M+H^+]$ 391.1683, found 391.1672.

1,2-Diethyl-4-(4-fluorophenyl)-5-[2-(*S*)-(α-methylbenzylamino)pyrimidin-4-yl]-1,2-dihydro-pyrazol-3-one; $[\alpha]^{25}_D = +74°$ (*c* 0.035, MeOH); ^{1}H NMR (300MHz, $CDCl_3$) δ 8.23 (d, *J* = 5.1 Hz, 1H), 7.42 – 7.29 (m, 2H), 7.69 (t, *J* = 8.8 Hz, 2H), 6.43 (d, *J* = 5.1 Hz, 1H), 5.33 (m, 1H), 4.15 (m, 1H), 4.05 – 3.75 (br s, 2H), 3.75 – 3.34 (br s, 2H), 1.61 (s, 3H), 1.33 – 1.28 (m, 6H); MS-ESI *m/z* 432 $[M+H]^+$; HRMS *m/z* calcd for $C_{25}H_{27}FN_5O$ $[M+H^+]$ 432.2200, found 432.2182.

1,2-Diethyl-4-(4-fluorophenyl)-5-[2-(*S*)-(1-methyl-2-methoxyethylamino)pyrimidin-4-yl]-1,2-dihydropyrazol-3-one; $[\alpha]^{25}_D$ = +58° (*c* 0.105, MeOH); ^{1}H NMR (300MHz, $CDCl_3$) δ 8.26 (d, *J* = 5.1 Hz, 1H), 7.40 (dd, *J* = 5.5, 8.8 Hz, 2H), 7.00 (t, *J* = 8.8 Hz, 2H), 6.45 (d, *J* = 5.1 Hz, 1H), 5.68 (br s, 1H), 4.29 (m, 1H), 4.01 (q, *J* = 7.1 Hz, 2H), 3.87 (q, *J* = 6.9 Hz, 2H), 3.47 (m, 1H), 3.41 (s, 3H), 1.37 – 1.29 (m, 6H), 0.929 (t, *J* = 6.9 Hz, 3H); MS-ESI *m/z* 400 $[M+H]^+$; HRMS *m/z* calcd for $C_{21}H_{27}FN_6O_2$ $[M+H^+]$ 400.2149, found 400.2131.

1,2-Dimethyl-4-(4-fluorophenyl)-5-[2-[(*N*-propanesulfonylpiperidin-4-yl)amino]-pyrimidin-4-yl]-1,2-dihydro-pyrazol-3-one; ^{1}H NMR (300MHz, $CDCl_3$) δ 8.24 (d, *J* = 4.8 Hz, 1H), 7.36 (m, 2H), 6.98 (t, *J* = 9 Hz, 2H), 6.38 (d, *J* = 5.1 Hz,1H), 5.26 (d, *J* = 7.2 Hz, 1H), 4.16 (m, 1H), 3.51 (s, 3H) 3.35 (s, 3H), 1.27 (d, *J* = 6.3, 6H); MS-APCI *m/z* 342 $[M+H]^+$; HRMS *m/z* calcd for $C_{18}H_{21}FN_5O$ $[M+H^+]$ 342.1730, found 372.1728.

Non-limiting examples of other compounds comprising the second aspect of Category IV include:

1,2-Diethyl-4-(4-fluorophenyl)-5-[2-(*S*)-(α-methylbenzylamino)pyrimidin-4-yl]-1,2-dihydropyrazol-3-one;

1,2-Dimethyl-4-(4-fluorophenyl)-5-[2-(thiazole-2-ylamino)pyrimidin-4-yl]-1,2-dihydro-pyrazol-3-one;

1,2-Diethyl-4-(4-fluorophenyl)-5-[2-(benzimidazol-2-ylamino)pyrimidin-4-yl]-1,2-dihydro-pyrazol-3-one.

Other compounds of the present invention, not directly encompassed within the herein above defined categories, which can be prepared by the procedures or modifications thereof disclosed herein above, include the following.

5-(2-Phenoxypyrimidin-4-yl)-4-(4-fluorophenyl)-1,2-dihydropyrazol-3-one;

2-Benzothiazol-2-yl-4-(4-fluorophenyl)-5-[2-(1-phenylethylamino)-pyrimidin-4-yl]-1,2-dihydropyrazol-3-one;

4-(4-Fluorophenyl)-1-(2-methoxyethyl)-5-[2-(2-methoxy-1-methylethylamino)pyrimidin-4-yl]-2-methyl-1,2-dihydropyrazol-3-one;

4-(4-Fluorophenyl)-1-(2-methoxyethyl)-5-[2-(1-phenylethylamino)-pyrimidin-4-yl]-2-methyl-1,2-dihydropyrazol-3-one;

4-(4-Fluorophenyl)-1-(2-methoxyethyl)-5-(2-phenoxypyrimidin-4-yl)-2-methyl-1,2-dihydropyrazol-3-one;

4-(4-Fluorophenyl)-1-methyl-5-[2-methoxypyrimidin-4-yl]-2-piperidin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-Fluorophenyl)-1-(piperidin-4-yl)-5-[2-(2-methoxy-1-methylethylamino)pyrimidin-4-yl]-2-phenyl-1,2-dihydropyrazol-3-one;

4-(4-Fluorophenyl)-1-(piperidin-4-yl)-5-[2-(2-methoxy-1-methylethylamino)pyrimidin-4-yl]-2-(4-chloro)phenyl-1,2-dihydropyrazol-3-one;

4-(4-Fluorophenyl)-2-(2-methoxyethyl)-5-[2-(2-methoxy-1-methylethylamino)pyrimidin-4-yl]-1-methyl-1,2-dihydropyrazol-3-one;

4-(4-Fluorophenyl)-2-(2-methoxyethyl)-5-(2-phenoxypyrimidin-4-yl)-1-methyl-1,2-dihydropyrazol-3-one;

4-(4-Fluorophenyl)-2-(2-methoxyethyl)-5-[2-(2-hydroxy-1,2-dimethylpropylamino)-pyrimidin-4-yl]-1-methyl-1,2-dihydropyrazol-3-one;

2-(4-chlorophenyl)-4-(4-fluorophenyl)-5-[2-(1-phenylethylamino)-pyrimidin-4-yl]-1,2-dihydropyrazol-3-one;

4-(4-Fluorophenyl)-1-methoxymethyl-5-(2-phenyoxypyrimidin-4-yl)-1,2-dihydropyrazol-3-one;

1-(Piperidin-4-yl)-2-methyl-4-(4-fluorophenyl)-5-[2-(tetrahydropyran-4-yl)pyrimidin-4-yl]-1,2-dihydro-pyrazol-3-one.

Compounds listed and described herein above have been found in many instances to exhibit activities (IC_{50} in the cell based assay described herein below or ones which are referenced herein) at a level below 1 micromolar (μM).

The compounds of the present invention are capable of effectively blocking the production of inflammatory cytokine production from cells, which thereby allows for the mitigation, alleviation, control, abatement, retardation, or prevention of one or more disease states or syndromes which are related to the extracellular release of one or more cytokines. Inflammatory disease states include those which are related to the following non-limiting examples:

i) Interleukin-1 (IL-1): implicated as the molecule responsible for a large number of disease states, *inter alia*, rheumatoid arthritis, osteoarthritis, as well as other disease states which relate to connective tissue degradation.

ii) Cycloxygenase-2 (COX-2): inhibitors of cytokine release are proposed as inhibitors of inducible COX-2 expression, which has been shown to be increased by cytokines. M. K. O'Banion et al., *Proc. Natl. Acad. Sci. U.S.A.*, **89**, 4888 (1998).

iii) Tumor Necrosis Factor–α (TNF-α): This pro-inflammatory cytokine is suggested as an important mediator in many disease states or syndromes, *inter alia*, rheumatoid arthritis, osteoarthritis, inflammatory bowel disease (IBS), septic shock, cardiopulmonary dysfunction, acute respiratory disease, and cachexia.

Each of the disease states or conditions which the formulator desires to treat may require differing levels or amounts of the compounds described herein to obtain a therapeutic level. The

formulator can determine this amount by any of the known testing procedures known to the artisan.

The present invention further relates to forms of the present compounds, which under normal human or higher mammalian physiological conditions, release the compounds described herein. One iteration of this aspect includes the pharmaceutically acceptable salts of the analogs described herein. The formulator, for the purposes of compatibility with delivery mode, excipients, and the like, can select one salt form of the present analogs over another since the compounds themselves are the active species which mitigate the disease processes described herein.

Related to this aspect are the various precursor of "pro-drug" forms of the analogs of the present invention. It may be desirable to formulate the compounds of the present invention as a chemical species which itself is not active against the cytokine activity described herein, but instead are forms of the present analogs which when delivered to the body of a human or higher mammal will undergo a chemical reaction catalyzed by the normal function of the body, *inter alia*, enzymes present in the stomach, blood serum, said chemical reaction releasing the parent analog. The term "pro-drug" relates to these species which are converted *in vivo* to the active pharmaceutical.

FORMULATIONS

The present invention also relates to compositions or formulations which comprise the inflammatory cytokine release-inhibiting compounds according to the present invention. In general, the compositions of the present invention comprise:

a) an effective amount of 1,2-dihydropyrazol-3-ones according to the present invention which are effective for inhibiting release of inflammatory cytokines; and

b) one or more pharmaceutically acceptable excipients.

For the purposes of the present invention the term "excipient" and "carrier" are used interchangeably throughout the description of the present invention and said terms are defined herein as, "ingredients which are used in the practice of formulating a safe and effective pharmaceutical composition."

The formulator will understand that excipients are used primarily to serve in delivering a safe, stable, and functional pharmaceutical, serving not only as part of the overall vehicle for delivery but also as a means for achieving effective absorption by the recipient of the active ingredient. An excipient may fill a role as simple and direct as being an inert filler, or an excipient as used herein may be part of a pH stabilizing system or coating to insure delivery of the ingredients safely to the stomach. The formulator can also take advantage of the fact the compounds of the present invention have improved cellular potency, pharmacokinetic properties, as well as improved oral bioavailability.

The present invention also relates to compositions or formulations which comprise a precursor or "pro-drug" form of the inflammatory cytokine release-inhibiting compounds according to the present invention. In general, these precursor-comprising compositions of the present invention comprise:

a) an effective amount of one or more derivatives of bicyclic pyrazolones according to the present invention which act to release *in vivo* the corresponding analog which is effective for inhibiting release of inflammatory cytokines; and

b) one or more pharmaceutically acceptable excipients.

METHOD OF USE

The present invention also relates to a method for controlling the level of one or more inflammation inducing cytokines, *inter alia*, interleukin-1 (IL-1), Tumor Necrosis Factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-8 (IL-8) and thereby controlling, mediating, or abating disease states affected by the levels of extracellular inflammatory cytokines. The present method comprises the step of administering to a human or higher mammal an effective amount of a composition comprising one or more of the inflammatory cytokine inhibitors according to the present invention.

Because the inflammatory cytokine inhibitors of the present invention can be delivered in a manner wherein more than one site of control can be achieved, more than one disease state can be modulated at the same time. Non-limiting examples of diseases which are affected by control or inhibition of inflammatory cytokine inhibitors, thereby modulating excessive cytokine activity, include osteoarthritis, rheumatoid arthritis, diabetes, human Immunodeficiency virus (HIV) infection.

PROCEDURES

The compounds of the present invention can be evaluated for efficacy, for example, measurements of cytokine inhibition constants, K_i, and IC_{50} values can be obtained by any method chosen by the formulator.

Non-limiting examples of suitable assays include:

i) UV-visible substrate enzyme assay as described by L. Al Reiter, *Int. J. Peptide Protein Res.*, **43**, 87-96 (1994).

ii) Fluorescent substrate enzyme assay as described by Thornberry et al., *Nature*, **356**, 768-774 (1992).

iii) PBMC Cell assay as described in U.S. 6,204,261 B1 Batchelor et al., issued March 20, 2001.

Each of the above citations is included herein by reference.

In addition, Tumor Necrosis Factor, TNF-α, inhibition can be measured by utilizing lipopolysaccharide (LPS) stimulated human monocytic cells (THP-1) as described in:

i) K. M. Mohler et al., "Protection Against a Lethal Dose of Endotoxin by an Inhibitor of Tumour Necrosis Factor Processing", *Nature*, **370**, pp 218-220 (1994).

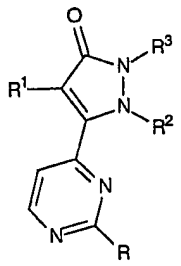
ii) U.S. 6,297,381 B1 Cirillo et al., issued October 2, 2001, incorporated by reference and reproduced herein below in relevant portion thereof.

The inhibition of cytokine production can be observed by measuring inhibition of TNF-α in lipopolysaccharide stimulated THP cells. All cells and reagents are diluted in RPMI 1640 with phenol red and L-glutamine, supplemented with additional L-glutamine (total: 4 mM), penicillin and streptomycin (50 units/mL each) and fetal bovine serum (FBS 3%) (GIBCO, all conc. Final). Assay is performed under sterile conditions, only test compound preparation is non-sterile. Initial stock solutions are made in DMSO followed by dilution into RPMI 1640 2-fold higher than the desired final assay concentration. Confluent THP.1 cells (2×10^7 cells/mL, final conc.; American Type Culture Company, Rockville, Md.) are added to 96 well polypropylene round bottomed culture plates (Costar 3790; sterile) containing 125 µL test compound (2-fold concentrated) or DMSO vehicle (controls, blanks). DMSO concentration should not exceed 0.2% final. Cell mixture is allowed to preincubate for 30 minutes at 37 °C, 5% CO_2 prior to stimulation with lipopolysaccharide (LPS, 1 µg/mL final; Sigma L-2630, from *E. coli* serotype 0111.B4; stored as 1 mg/mL stock in endotoxin screened diluted H_2O vehicle at –80 °C). Blanks (unstimulated) receive H_2O vehicle; final incubation volume is 250 µL. Incubation (4 hours) proceeds as described above. Assay is to be terminated by centrifuging plates 5 minutes at room temperature, 1600 rpm (4033 g); supernatants are then transferred to clean 96 well plates and stored at –80 °C until analyzed for human TNF-α by a commercially available ELISA kit (Biosource #KHC3015, Camarillo, Ca.). The calculated IC_{50} value is the concentration of the test compound that caused a 50% decrease in the maximal TNF-α production.

While particular embodiments of the present invention have been illustrated and described, it would be obvious to those skilled in the art that various other changes and modifications can be made without departing from the spirit and scope of the invention. It is therefore intended to cover in the appended claims all such changes and modifications that are within the scope of this invention.

What is claimed is:

1. A compound, including all enantiomeric and diasteriomeric forms and pharmaceutically acceptable salts thereof, said compound having the formula:



wherein R is:

a) $-O[CH_2]_nR^4$; or

b) $-NR^{5a}R^{5b}$;

R^4 is substituted or unsubstituted C_1-C_{10} linear, branched, or cyclic alkyl; substituted or unsubstituted aryl; substituted or unsubstituted heterocyclic; or substituted or unsubstituted heteroaryl; the index n is from 0 to 5;

R^{5a} and R^{5b} are each independently:

a) hydrogen; or

b) $-[C(R^{6a}R^{6b})]_mR^7$;

each R^{6a} and R^{6b} is independently:

i) hydrogen;

ii) $-OR^8$;

iii) $-N(R^8)_2$;

iv) $-CO_2R^8$;

v) $-CON(R^8)_2$;

vi) substituted or unsubstituted C_1-C_4 linear, branched, or cyclic alkyl;

vii) and mixtures thereof;

R^7 is

i) hydrogen;

ii) substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl;

iii) substituted or unsubstituted heterocyclic;

iv) substituted or unsubstituted aryl;

v) substituted or unsubstituted heteroaryl;

vi) $-OR^8$;

vii) $-N(R^8)_2$;

viii) $-CO_2R^8$; and

ix) $-CON(R^8)_2$;

R^8 is hydrogen, a water-soluble cation, C_1-C_4 alkyl, or substituted or unsubstituted aryl;

the index m is from 0 to 5;

R^1 is substituted phenyl;

each R^2 and R^3 unit is independently selected from the group consisting of:

a) hydrogen; and

b) substituted or unsubstituted C_1-C_{10} hydrocarbyl selected from the group consisting of:

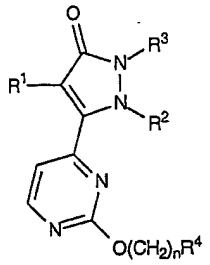
i) C_1-C_{10} linear, branched or cyclic alkyl;

ii) C_6-C_{10} aryl;

iii) C_1-C_{10} heterocyclic;

iv) C_1-C_{10} heteroaryl.

2. A compound according to Claim 1 having the formula:



wherein R^4 is substituted or unsubstituted:

i) C_1-C_4 alkyl;

ii) C_3-C_{10} carbocyclic;

iii) C_1-C_{10} heterocyclic;

iv) C_6-C_{10} aryl; or

v) C_1-C_{10} heteroaryl;

the index n is from 0 to 5.

3. A compound according to either Claim 1 or 2 wherein R^1 is 4-fluorophenyl, R^2 and R^3 are each independently substituted or unsubstituted C_1-C_{10} hydrocarbyl selected from:

i) C_1-C_{10} linear, branched or cyclic alkyl;

ii) C_1-C_{10} aryl;

iii) C_1-C_{10} heterocyclic;

iv) C_1-C_{10} heteroaryl; and

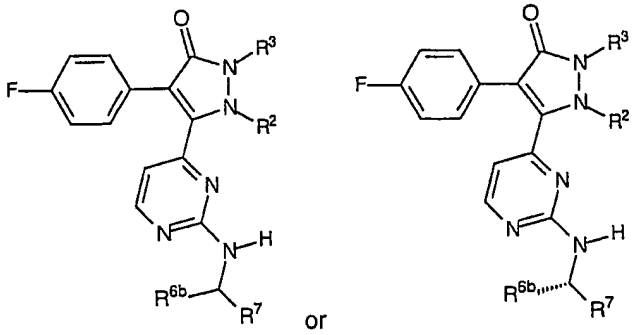
R^4 is substituted or unsubstituted aryl and the index n is 0 or 1.

4. A compound according to any of Claims 1-3 wherein R^2 is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, and cyclopropyl-methyl, R^3 is selected from the group consisting of substituted or unsubstituted piperidin-4-yl, *N*-methylpiperidin-4-yl, morpholin-4-yl, and *N*-methylmorpholin-4-yl, and R^4 is selected from the group consisting of phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,6-difluorophenyl, 2-cyanophenyl, 3-cyanophenyl, 2-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-methylphenyl, 4-methylphenyl, 2,4-dimethylphenyl, 3-N-acetyl-aminophenyl, 2-methoxyphenyl, 4-methoxyphenyl, and 3-benzo[1,3]dioxol-5-yl.

5. A compound according to any of Claims 1-3 wherein R^2 is selected from the group consisting of substituted or unsubstituted piperidin-4-yl, *N*-methylpiperidin-4-yl, morpholin-4-yl, and *N*-methylmorpholin-4-yl, R^3 is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, and cyclopropyl-methyl, and R^4 is selected from the group consisting of phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,6-difluorophenyl, 2-cyanophenyl, 3-cyanophenyl, 2-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-methylphenyl, 4-methylphenyl, 2,4-dimethylphenyl, 3-N-acetyl-aminophenyl, 2-methoxyphenyl, 4-methoxyphenyl, and 3-benzo[1,3]dioxol-5-yl.

6. A compound according to any of Claims 1-4 wherein R^2 and R^3 are both methyl or both ethyl, R^4 is selected from the group consisting of phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,6-difluorophenyl, 2-cyanophenyl, 3-cyanophenyl, 2-trifluoromethyl-phenyl, 4-trifluoromethylphenyl, 2-methylphenyl, 4-methylphenyl, 2,4-dimethylphenyl, 3-N-acetyl-aminophenyl, 2-methoxyphenyl, 4-methoxyphenyl, and 3-benzo[1,3]dioxol-5-yl, and the index n is 0 or 1.

7. A compound according to Claim 1 having the formula:



or

wherein R^2 and R^3 are each independently substituted or unsubstituted C_1-C_{10} hydrocarbyl selected from:

i) C_1-C_{10} linear, branched or cyclic alkyl;

ii) C_6-C_{10} aryl;

iii) C_1-C_{10} heterocyclic; and

iv) C_1-C_{10} heteroaryl;

R^{6b} is hydrogen, C_1-C_4 alkyl, or $-CO_2R^8$; R^8 is hydrogen, methyl, or a salt forming cation;

R^7 is selected from the group consisting of:

i) hydrogen;

ii) substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl;

iii) substituted or unsubstituted C_6-C_{10} aryl;

iv) substituted or unsubstituted C_1-C_{10}heterocyclic; and

v) substituted or unsubstituted C_1-C_{10} heteroaryl.

8. A compound according to Claims 1 or 7 wherein R^2 is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, and cyclopropyl-methyl, R^3 is selected from the group consisting of substituted or unsubstituted piperidin-4-yl, *N*-methylpiperidin-4-yl, morpholin-4-yl, and *N*-methylmorpholin-4-yl, R^{6b} is hydrogen, and R^7 is substituted or unsubstituted C_6-C_{10} aryl.

9. A compound according to Claims 1 or 7 wherein R^2 is selected from the group consisting of substituted or unsubstituted piperidin-4-yl, *N*-methylpiperidin-4-yl, morpholin-4-yl, and *N*-methylmorpholin-4-yl, R^3 is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, and cyclopropyl-methyl, R^{6b} is hydrogen, and R^7 is substituted or unsubstituted C_6-C_{10} aryl.

10. A compound according to Claims 1 or 7 wherein R^2 and R^3 are both methyl or both ethyl, R^{6b} is hydrogen, methyl, or ethyl, and R^7 is substituted or unsubstituted C_6-C_{10} aryl.

11. A compound according to any of Claim 7-10 wherein R^7 is selected from the group consisting of methyl, ethyl, cyclopropyl, cyclohexyl, hydroxymethyl, methoxymethyl, 1-methoxyethyl, 1-methoxy-1-methyl-ethyl, 1-hydroxy-1-methyl-ethyl, 1-hydroxyethyl, phenyl, 4-fluorophenyl, 2-aminophenyl, 2-methylphenyl, 4-methylphenyl, 4-methoxy-phenyl, 4-(methanesulfonyl)phenyl, 4-(ethanesulfonyl)phenyl, 4-(propanesulfonyl)phenyl, 3-benzo[1,3]dioxol-5-yl, pyridin-2-yl, pyridin-3-yl, and pyridin-4-yl.

12. A compound according to Claim 1 selected from the group consisting of:

4-(4-fluorophenyl)-2-methyl-5-(2-phenoxy-pyrimidin-4-yl)-1-piperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-[2-(2-fluorophenoxy)pyrimidin-4-yl]-1-piperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-[2-(3-fluorophenoxy)pyrimidin-4-yl]-1-piperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-[2-(4-fluorophenoxy)pyrimidin-4-yl]-1-piperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-2-ethyl-5-(2-phenoxy-pyrimidin-4-yl)-1-piperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-2-ethyl-5-[2-(2-fluorophenoxy)pyrimidin-4-yl]-1-piperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-2-ethyl-5-[2-(3-fluorophenoxy)pyrimidin-4-yl]-1-piperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-2-ethyl-5-[2-(4-fluorophenoxy)pyrimidin-4-yl]-1-piperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-(2-phenoxy-pyrimidin-4-yl)-1-morpholin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-[2-(2-fluorophenoxy)pyrimidin-4-yl]-1-morpholin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-[2-(3-fluorophenoxy)pyrimidin-4-yl]-1-morpholin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-[2-(4-fluorophenoxy)pyrimidin-4-yl]-1-morpholin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-2-ethyl-5-(2-phenoxy-pyrimidin-4-yl)-1-morpholin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-2-ethyl-5-[2-(2-fluorophenoxy)pyrimidin-4-yl]-1-morpholin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-2-ethyl-5-[2-(3-fluorophenoxy)pyrimidin-4-yl]-1-morpholin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-2-ethyl-5-[2-(4-fluorophenoxy)pyrimidin-4-yl]-1-morpholin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-(2-phenoxy-pyrimidin-4-yl)-1-*N*-methylpiperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-[2-(2-fluorophenoxy)pyrimidin-4-yl]-1-*N*-methylpiperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-[2-(3-fluorophenoxy)pyrimidin-4-yl]-1-*N*-methylpiperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-[2-(4-fluorophenoxy)pyrimidin-4-yl]-1-*N*-methylpiperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-2-ethyl-5-(2-phenoxy-pyrimidin-4-yl)-1-*N*-methylpiperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-2-ethyl-5-[2-(2-fluorophenoxy)pyrimidin-4-yl]-1-*N*-methylpiperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-2-ethyl-5-[2-(3-fluorophenoxy)pyrimidin-4-yl]-1-*N*-methylpiperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-2-ethyl-5-[2-(4-fluorophenoxy)pyrimidin-4-yl]-1-*N*-methylpiperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-1-methyl-5-(2-phenoxy-pyrimidin-4-yl)-2-piperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-1-methyl-5-[2-(2-fluorophenoxy)pyrimidin-4-yl]-2-piperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-1-methyl-5-[2-(3-fluorophenoxy)pyrimidin-4-yl]-2-piperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-1-methyl-5-[2-(4-fluorophenoxy)pyrimidin-4-yl]-2-piperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-1-ethyl-5-(2-phenoxy-pyrimidin-4-yl)-2-piperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-1-ethyl-5-[2-(2-fluorophenoxy)pyrimidin-4-yl]-2-piperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-1-ethyl-5-[2-(3-fluorophenoxy)pyrimidin-4-yl]-2-piperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-1-ethyl-5-[2-(4-fluorophenoxy)pyrimidin-4-yl]-2-piperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-1-methyl-5-(2-phenoxy-pyrimidin-4-yl)-2-morpholin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-1-methyl-5-[2-(2-fluorophenoxy)pyrimidin-4-yl]-2-morpholin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-1-methyl-5-[2-(3-fluorophenoxy)pyrimidin-4-yl]-2-morpholin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-1-methyl-5-[2-(4-fluorophenoxy)pyrimidin-4-yl]-2-morpholin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-1-ethyl-5-(2-phenoxy-pyrimidin-4-yl)-2-morpholin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-1-ethyl-5-[2-(2-fluorophenoxy)pyrimidin-4-yl]-2-morpholin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-1-ethyl-5-[2-(3-fluorophenoxy)pyrimidin-4-yl]-2-morpholin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-1-ethyl-5-[2-(4-fluorophenoxy)pyrimidin-4-yl]-2-morpholin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-1-methyl-5-(2-phenoxy-pyrimidin-4-yl)-2-*N*-methylpiperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-1-methyl-5-[2-(2-fluorophenoxy)pyrimidin-4-yl]-2-*N*-methylpiperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-1-methyl-5-[2-(3-fluorophenoxy)pyrimidin-4-yl]-2-*N*-methylpiperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-1-methyl-5-[2-(4-fluorophenoxy)pyrimidin-4-yl]-2-*N*-methylpiperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-1-ethyl-5-(2-phenoxy-pyrimidin-4-yl)-2-*N*-methylpiperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-1-ethyl-5-[2-(2-fluorophenoxy)pyrimidin-4-yl]-2-*N*-methylpiperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-1-ethyl-5-[2-(3-fluorophenoxy)pyrimidin-4-yl]-2-*N*-methylpiperidin-4-yl-1,2-dihydro-pyrazol-3-one;

4-(4-fluorophenyl)-1-ethyl-5-[2-(4-fluorophenoxy)pyrimidin-4-yl]-2-*N*-methylpiperidin-4-yl-1,2-dihydro-pyrazol-3-one

1,2-dimethyl-4-(4-fluorophenyl)- 5-(2-phenoxypyrimidin-4-yl)-1,2-dihydropyrazol-3-one;

1,2-diethyl-4-(4-fluorophenyl)-5-(2-phenoxypyrimidin-4-yl)-1,2-dihydropyrazol-3-one;

1,2-dimethyl-4-(4-fluorophenyl)- 5-[2-(2-fluorophenoxy)pyrimidin-4-yl]-1,2-dihydropyrazol-3-one;

1,2-diethyl-4-(4-fluorophenyl)-5-[2-(2-fluorophenoxy)pyrimidin-4-yl]-1,2-dihydropyrazol-3-one;

1,2-dimethyl-4-(4-fluorophenyl)- 5-[2-(3-fluorophenoxy)pyrimidin-4-yl]-1,2-dihydropyrazol-3-one;

1,2-diethyl-4-(4-fluorophenyl)-5-[2-(3-fluorophenoxy)pyrimidin-4-yl]-1,2-dihydropyrazol-3-one;

1,2-dimethyl-4-(4-fluorophenyl)- 5-[2-(4-fluorophenoxy)pyrimidin-4-yl]-1,2-dihydropyrazol-3-one;

1,2-diethyl-4-(4-fluorophenyl)-5-[2-(4-fluorophenoxy)pyrimidin-4-yl]-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-{2-[(phenyl)methylamino]-pyrimidin-4-yl}-1-piperidin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-{2-[(2-fluorophenyl)methylamino]-pyrimidin-4-yl}-1-piperidin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-{2-[(3-fluorophenyl)methylamino]-pyrimidin-4-yl}-1-piperidin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-{2-[(4-fluorophenyl)methylamino]-pyrimidin-4-yl}-1-piperidin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-{2-[(2-aminophenyl)methylamino]-pyrimidin-4-yl}-1-piperidin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-{2-[(3-aminophenyl)methylamino]-pyrimidin-4-yl}-1-piperidin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-{2-[(4-aminophenyl)methylamino]-pyrimidin-4-yl}-1-piperidin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-{2-[(phenyl)methylamino]-pyrimidin-4-yl}-1-morpholin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-{2-[(2-fluorophenyl)methylamino]-pyrimidin-4-yl}-1-morpholin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-{2-[(3-fluorophenyl)methylamino]-pyrimidin-4-yl}-1-morpholin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-{2-[(4-fluorophenyl)methylamino]-pyrimidin-4-yl}-1-morpholin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-{2-[(2-aminophenyl)methylamino]-pyrimidin-4-yl}-1-morpholin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-{2-[(3-aminophenyl)methylamino]-pyrimidin-4-yl}-1-morpholin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-{2-[(4-aminophenyl)methylamino]-pyrimidin-4-yl}-1-morpholin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-{2-[(phenyl)methylamino]-pyrimidin-4-yl}-1-(*N*-acetyl)-piperidin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-{2-[(2-fluorophenyl)methylamino]-pyrimidin-4-yl}-1-(*N*-acetyl)-piperidin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-{2-[(3-fluorophenyl)methylamino]-pyrimidin-4-yl}-1-(*N*-acetyl)-piperidin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-{2-[(4-fluorophenyl)methylamino]-pyrimidin-4-yl}-1-(*N*-acetyl)-piperidin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-{2-[(2-aminophenyl)methylamino]-pyrimidin-4-yl}-1-(*N*-acetyl)-piperidin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-{2-[(3-aminophenyl)methylamino]-pyrimidin-4-yl}-1-(*N*-acetyl)-piperidin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-2-methyl-5-{2-[(4-aminophenyl)methylamino]-pyrimidin-4-yl}-1-(*N*-acetyl)-piperidin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-5-[2-(*S*)-(α-methylbenzylamino)pyrimidin-4-yl]-1-methyl-2-piperidin-4-yl-1,2-dihydropyrazol-3-one;

(4-{4-(4-fluorophenyl)-2-methyl-5-oxo-3-[2-(*S*)-(α-methylbenzylamino)pyrimidin-4-yl]-2,5-dihydropyrazol-1-yl}piperidin-1-yl) acetic acid;

2-(4-{4-(4-fluorophenyl)-2-methyl-5-oxo-3-[2-(*S*)-(α-methylbenzylamino)pyrimidin-4-yl]-2,5-dihydropyrazol-1-yl}piperidin-1-yl)-2-methyl propionic acid;

(4-{4-(4-fluorophenyl)-2-methyl-5-oxo-3-[2-(*S*)-(α-methylbenzylamino)pyrimidin-4-yl]-2,5-dihydropyrazol-1-yl}piperidin-1-yl) acetic acid ethyl ester;

2-(4-{4-(4-fluorophenyl)-2-methyl-5-oxo-3-[2-(*S*)-(α-methylbenzylamino)pyrimidin-4-yl]-2,5-dihydropyrazol-1-yl}piperidin-1-yl)-2-methyl propionic acid ethyl ester;

4-(4-fluorophenyl)-5-[2-(*S*)-(α-methylbenzylamino)pyrimidin-4-yl]-2-methyl-1-piperidin-4-yl-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-5-[2-(*S*)-(α-methylbenzylamino)pyrimidin-4-yl]-1,2-dimethyl-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-5-[2-(2-hydroxy-1-(*S*)-methyl-2-methylpropylamino)-pyrimidin-4-yl]-1,2-dimethyl-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-5-[2-(2-methoxy-1-(*S*)-methylethylamino)-pyrimidin-4-yl]-1,2-dimethyl-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-5-[2-(*S*)-(α-methylbenzylamino)pyrimidin-4-yl]-1-methyl-2-(2-methoxyethyl)-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-5-[2-(*S*)-(α-methylbenzylamino)pyrimidin-4-yl]-2-methyl-1-(2-methoxyethyl)-1,2-dihydropyrazol-3-one;

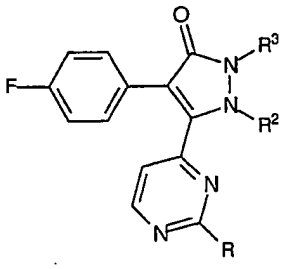
4-(4-fluorophenyl)-5-[2-(2-hydroxy-1-(*S*)-methyl-2-methylpropylamino)-pyrimidin-4-yl]-1-methyl-2-(2-methoxyethyl)-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-5-[2-(2-hydroxy-1-(*S*)-methyl-2-methylpropylamino)-pyrimidin-4-yl]-2-methyl-1-(2-methoxyethyl)-1,2-dihydropyrazol-3-one;

4-(4-fluorophenyl)-5-[2-(2-methoxy-1-(*S*)-methylethylamino)-pyrimidin-4-yl]-2-methyl-1-piperidin-4-yl -1,2-dihydropyrazol-3-one; and

4-(4-fluorophenyl)-5-[2-(2-methoxy-1-(*S*)-methylethylamino)-pyrimidin-4-yl]-1-methyl-2-piperidin-4-yl -1,2-dihydropyrazol-3-one.

13. A compound, including all enantiomeric and diasteriomeric forms and pharmaceutically acceptable salts thereof, said compound having the formula:



wherein R is $-NH[C(R^{6a}R^{6b})]R^7$
each R^{6a} and R^{6b} is independently methyl, ethyl, and mixtures thereof;
R^7 hydrogen; substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl; substituted or unsubstituted aryl; and substituted or unsubstituted heteroaryl;
each R^2 and R^3 unit is independently substituted or unsubstituted C_1-C_{10} linear, branched or cyclic alkyl; substituted or unsubstituted C_1-C_{10} heterocyclic; and mixtures thereof.

14. A compound according to Claim 3 wherein R is selected from the group consisting of ((*S*)-1-methylpropylamino, (*S*)-1-methyl-1-methoxyethylamino, (*S*)-1-methyl-2-(*S*)-methoxy-propylamino, (*S*)-1,2-methyl-2-methoxypropylamino, *S*)-1-ethylpropylamino, (*S*)-1-ethyl-1-methoxyethylamino, (*S*)-1-ethyl-2-(*S*)-methoxypropylamino, (*S*)-1-ethyl-2-methyl-2-methoxypropylamino, *S*)-(α)-methylbenzylamino, (*S*)-1-methyl-1-(4-fluorophenyl)methylamino, (*S*)-1-methyl-1-(2-aminophenyl)methylamino , (*S*)-1-methyl-1-(2-methylphenyl)methylamino , (*S*)-1-methyl-1-(4-methylphenyl)methylamino, (*S*)-1-methyl-1-(4-methoxyphenyl)-methylamino, (*S*)-(α)-ethylbenzylamino, (*S*)-1-(4-fluorophenyl)ethylamino, (*S*)-1-(2-aminophenyl)-ethylamino , (*S*)-1-ethyl-1-(2-methylphenyl)amino, (*S*)-1-(4-methylphenyl)-ethylamino, (*S*)-1-(4-methoxyphenyl)-ethylamino, (*S*)-1-(4-fluorophenyl)-2-hydroxyethylamino.

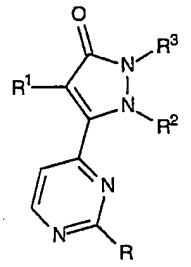
15. A compound according to either Claim 13 or 14 wherein R^2 is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, and cyclopropyl-methyl, and R^3 is selected from the group consisting of substituted or unsubstituted piperidin-4-yl, *N*-methylpiperidin-4-yl, morpholin-4-yl, and *N*-methylmorpholin-4-yl.

16. A compound according to either Claim 13 or 14 wherein R^2 is selected from the group consisting of substituted or unsubstituted piperidin-4-yl, *N*-methylpiperidin-4-yl, morpholin-4-yl, and *N*-methylmorpholin-4-yl, and R^3 is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, and cyclopropyl-methyl.

17. A compound according to either Claim 13 or 14 wherein R^2 and R^3 are both methyl or both ethyl.

18. A composition comprising

A) an effective amount of one or more 1,2-dihydropyrazol-3-ones, all enantiomeric and diasteriomeric forms and pharmaceutically acceptable salts thereof, said compound having the formula:



wherein R is:

a) $-O[CH_2]_nR^4$; or

b) $-NR^{5a}R^{5b}$;

R^4 is substituted or unsubstituted C_1-C_{10} linear, branched, or cyclic alkyl; substituted or unsubstituted aryl; substituted or unsubstituted heterocyclic; or substituted or unsubstituted heteroaryl; the index n is from 0 to 5;

R^{5a} and R^{5b} are each independently:

a) hydrogen; or

b) $-[C(R^{6a}R^{6b})]_mR^7$;

each R^{6a} and R^{6b} is independently:

i) hydrogen;

ii) $-OR^8$;

iii) $-N(R^8)_2$;

iv) $-CO_2R^8$;

v) $-CON(R^8)_2$;

vi) substituted or unsubstituted C_1-C_4 linear, branched, or cyclic alkyl;

vii) and mixtures thereof;

R^7 is

i) hydrogen;

ii) substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl;

iii) substituted or unsubstituted heterocyclic;

iv) substituted or unsubstituted aryl;

v) substituted or unsubstituted heteroaryl;

vi) $-OR^8$;

vii) $-N(R^8)_2$;

viii) $-CO_2R^8$; and

ix) $-CON(R^8)_2$;

R^8 is hydrogen, a water-soluble cation, C_1-C_4 alkyl, or substituted or unsubstituted aryl;

the index m is from 0 to 5;

R^1 is substituted phenyl;

each R^2 and R^3 unit is independently selected from the group consisting of:

a) hydrogen; and

b) substituted or unsubstituted C_1-C_{10} hydrocarbyl selected from the group consisting of:

i) C_1-C_{10} linear, branched or cyclic alkyl;

ii) C_6-C_{10} aryl;

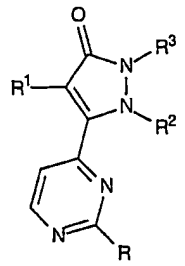
iii) C_1-C_{10} heterocyclic;

iv) C_1-C_{10} heteroaryl; and

B) one or more pharmaceutically acceptable excipients.

19. A method for inhibiting the extracellular release of inflammatory cytokines, said method comprising the step of administering to a human or higher mammal an effective amount of a pharmaceutical composition comprising:

A) an effective amount of one or more 1,2-dihydropyrazol-3-ones, all enantiomeric and diasteriomeric forms and pharmaceutically acceptable salts thereof, said compound having the formula:



wherein R is:

a) $-O[CH_2]_nR^4$; or

b) $-NR^{5a}R^{5b}$;

R^4 is substituted or unsubstituted C_1-C_{10} linear, branched, or cyclic alkyl; substituted or unsubstituted aryl; substituted or unsubstituted heterocyclic; or substituted or unsubstituted heteroaryl; the index n is from 0 to 5;

R^{5a} and R^{5b} are each independently:

a) hydrogen; or

b) $-[C(R^{6a}R^{6b})]_mR^7$;

each R^{6a} and R^{6b} is independently:

i) hydrogen;

ii) $-OR^8$;

iii) $-N(R^8)_2$;

iv) $-CO_2R^8$;

v) $-CON(R^8)_2$;

vi) substituted or unsubstituted C_1-C_4 linear, branched, or cyclic alkyl;

vii) and mixtures thereof;

R^7 is

i) hydrogen;

ii) substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl;

iii) substituted or unsubstituted heterocyclic;

iv) substituted or unsubstituted aryl;

v) substituted or unsubstituted heteroaryl;

vi) $-OR^8$;

vii) $-N(R^8)_2$;

viii) $-CO_2R^8$; and

ix) $-CON(R^8)_2$;

R^8 is hydrogen, a water-soluble cation, C_1-C_4 alkyl, or substituted or unsubstituted aryl;

the index m is from 0 to 5;

R^1 is substituted phenyl;

each R^2 and R^3 unit is independently selected from the group consisting of:

a) hydrogen; and

b) substituted or unsubstituted C_1-C_{10} hydrocarbyl selected from the group consisting of:

i) C_1-C_{10} linear, branched or cyclic alkyl;

ii) C_6-C_{10} aryl;

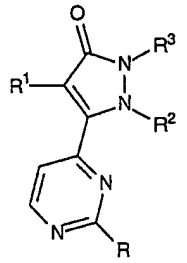
iii) C_1-C_{10} heterocyclic;

iv) C_1-C_{10} heteroaryl; and

B) one or more pharmaceutically acceptable excipients.

20. A method for controlling the level of one or more inflammation inducing cytokines selected from the group consisting of interleukin-1 (IL-1), Tumor Necrosis Factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-8 (IL-8) and thereby controlling, mediating, or abating disease states affected by the levels of these extracellular inflammatory cytokines, said method comprising the step of administering to a human or higher mammal an effective amount of a pharmaceutical composition comprising:

A) an effective amount of one or more 1,2-dihydropyrazol-3-ones, all enantiomeric and diasterlomeric forms and pharmaceutically acceptable salts thereof, said compound having the formula:



wherein R is:

a) $-O[CH_2]_nR^4$; or

b) $-NR^{5a}R^{5b}$;

R^4 is substituted or unsubstituted C_1-C_{10} linear, branched, or cyclic alkyl; substituted or unsubstituted aryl; substituted or unsubstituted heterocyclic; or substituted or unsubstituted heteroaryl; the index n is from 0 to 5;

R^{5a} and R^{5b} are each independently:

a) hydrogen; or

b) $-[C(R^{6a}R^{6b})]_mR^7$;

each R^{6a} and R^{6b} is independently:

i) hydrogen;

ii) $-OR^8$;

iii) $-N(R^8)_2$;

iv) $-CO_2R^8$;

v) $-CON(R^8)_2$;

vi) substituted or unsubstituted C_1-C_4 linear, branched, or cyclic alkyl;

vii) and mixtures thereof;

R^7 is

i) hydrogen;

ii) substituted or unsubstituted C_1-C_6 linear, branched, or cyclic alkyl;

iii) substituted or unsubstituted heterocyclic;

iv) substituted or unsubstituted aryl;

v) substituted or unsubstituted heteroaryl;

vi) $-OR^8$;

vii) $-N(R^8)_2$;

viii) $-CO_2R^8$; and

ix) $-CON(R^8)_2$;

R^8 is hydrogen, a water-soluble cation, C_1-C_4 alkyl, or substituted or unsubstituted aryl;

the index m is from 0 to 5;

R^1 is substituted phenyl;

each R^2 and R^3 unit is independently selected from the group consisting of:

a) hydrogen; and

b) substituted or unsubstituted C_1-C_{10} hydrocarbyl selected from the group consisting of:

i) C_1-C_{10} linear, branched or cyclic alkyl;

ii) C_6-C_{10} aryl;

iii) C_1-C_{10} heterocyclic;

iv) C_1-C_{10} heteroaryl; and

B) one or more pharmaceutically acceptable excipients.

INTERNATIONAL SEARCH REPORT

PCT/US 03/07635

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P29/00 C07D403/04 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 03 024971 A (THE PROCTER & GAMBLE COMPANY) 27 March 2003 (2003-03-27) claims 1-18	1-20
E	WO 03 024973 A (THE PROCTER & GAMBLE COMPANY) 27 March 2003 (2003-03-27) claims 1-14	1-20
E	WO 03 024970 A (THE PROCTER & GAMBLE COMPANY) 27 March 2003 (2003-03-27) claims 1-11	1-20
P,Y	WO 02 092573 A (VERTEX PHARMACEUTICALS INC.) 21 November 2002 (2002-11-21) claims 1-32	1-20

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 August 2003	04/09/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Herz, C

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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